

Re: updating all participating sites

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Mon 2/23/09 2:45 PM

To: RM Fleming (rmfmd7@hotmail.com)

Dr. Fleming,

This is the document I was thinking about. Please let me know the best 7-10 of these documents I should have on hand to show sestamibi is not super glue.

Thanks, Mike Hansen

To all participating sites using FH washout,

The following includes a list of information which should be helpful for all participating sites using the FH Washout protocol. Some of this information may be redundant; however, some of it has not been sent out before except in the form of a power point presentation which not everyone has received. I include this so everyone will have updated files and I encourage everyone to obtain copies of these publications. I am only including peer reviewed medical material and it does not include everything published on multiple post-stress imaging.

Peer reviewed publications directly proving that Sestamibi washes out of myocardial cells at different rates depending upon the presence or absence of ischemia. Sestamibi doesn't just go in and stick and stay there.
[SESTAMIBI IS NOT SUPERGLUE!]

- 1) Blumgart and Yens 1926, publish paper on "Circulation Time."
- 2) Maublant JC, Gachon P, Moins N. Hexakis (2-methoxy isobutylisonitrile) technetium-99m and thallium-201 chloride: uptake and release in cultured myocardial cells. J Nucl Med 1988; 29(1):48-54. Proves washout of sestamibi in non-ischemic tissue is 28 minutes (enough for 2 washouts in 55 minutes).
- 3) Li Q-S, Solot G, Frank TL, Wagner HN, and Becker LC. Myocardial redistribution of technetium-99m-methoxyisobutyl isonitrile (sestamibi), J Nucl Med 1990;31:1069-1075. Proves that sestamibi washes out (redistributes) even faster than the 28 minutes noted by Maublant, when ischemia is present.
- 4) Crane P, Laliberte R, Heminway S, Thoolen M, Orlandi C. Effect of mitochondrial viability and metabolism on technetium-99m-sestamibi myocardial retention. Eur J Nucl Med 1993;20:20-25. A study paid for by Dupont who owned sestamibi proves that the reason sestamibi washes out sooner in ischemic tissue than non-ischemic tissue, is that ischemic tissue has mitochondrial calcium overload which results in faster washout of sestamibi.

All these studies show sestamibi doesn't go in and stick like superglue; but, rather washes out in normal tissue in 28 minutes and even faster in regions with coronary artery disease.

Additionally published data in peer reviewed medical journals showing the clinical significance of using multiple images to look for washout (including heart failure, cardiomyopathies and vasospastic coronary artery disease)

1. Pace L, Catalano L, Del Vecchio S, et al. Washout of [99mTc] sestamibi in predicting response to chemotherapy in patients with multiple myeloma. *Q J Nucl Med Mol Imaging* 2005;49:281-5.
2. Hurwitz GA, Ghali SK, Husni M, et al. Pulmonary uptake of Technetium-99m-Sestamibi induced by dipyridamole-based stress or exercise. *J Nucl Med* 1998;39:339-45.
3. Hurwitz GA, Fox SP, Driedger AA, Willems C, Powe JE. Pulmonary uptake of sestamibi on early post-stress images: angiographic relationships, incidence and kinetics. *Nucl Med Commun* 1993;14:15-22. .
4. Saha M, Forrest TF, Brown KA. Lung uptake of technetium-99m-sestamibi: relation to clinical, exercise, hemodynamic, and left ventricular function variables. *J Nucl Cardiol* 1994;1:52-6.
5. Giubbini R, Bampini R, Milan E, et al. Evaluation of technetium-99m-sestamibi lung uptake: correlation with left ventricular function. *J Nucl Med* 1995;36:58-63.
6. Sugiura T, Takase H, Toriyama T, et al. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.
7. Kumita S, Seino Y, Cho K, et al. Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison with normal control. *Ann Nucl Med* 2002;16:237-42.
8. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. *J Nucl Cardiol* 2007;14:215-20.
9. Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.
10. Ikawa M, Kawai Y, Arakawa K, et al. Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of 99mTc-MIBI washout and 123I-BMIPP/99mTc-MIBI mismatch. *Mitochondrion* 2007;7:164-70.
11. Meissner K, Sperker B, Karsten C, et al. Expression and localization of P-glycoprotein in Human Heart: Effects of Cardiomyopathy. *J Histochem Cytochem* 2002;50:1351-6.
12. Ono S, Yamaguchi H, Takayama S, Kurabe A, Heito T. Rest delayed images on 99mTc-MIBI myocardial SPECT as a noninvasive screen for the diagnosis of vasospastic angina pectoris. *Kaku Igaku* 2002;39:117-24.
13. Ono S, Yakeishi Y, Yamaguchi H, et al. Enhanced regional washout of technetium-99m-sestamibi in patients with coronary spastic angina. *Ann Nucl Med* 2003;17:393-8.
14. Fukushima K, Momose M, Kondo C, et al. Myocardial kinetics of (201) Thallium, (99m) Tc-tetrofosmin, and (99m) Tc-sestamibi in an acute ischemia-reperfusion model using isolated rat heart. *Ann Nucl Med* 2007;21:267-73.
15. VanBrocklin HF, Hanrahan SM, Enas JD, et al. Mitochondrial avid radioprobes. Preparation and evaluation of 7'(2)-[125I]iodorotenone and 7'(Z)-[125I]iodorotenol. *Nucl Med Biol* 2007;34:109-16.
16. Tanaka R, Nakamura T, Chiba S, et al. Clinical implication of reverse redistribution on 99mTc-sestamibi images for evaluating ischemic heart disease. *Ann Nucl Med* 2006;20:349-56.
17. Liu Z, Johnson G 3rd, Beju D, Okada RD. Detection of myocardial viability in ischemic-reperfused rat hearts by Tc-99m sestamibi kinetics. *J Nucl Cardiol* 2001;8:677-86.
18. Shin WJ, Miller K, Stipp V, Mazour S. Reverse redistribution on dynamic exercise and dipyridamole stress technetium-99m-MIBI myocardial SPECT. *J Nucl Med* 1995;36:2053-5

19. Takeishi Y, Sukekawa H, Fujiwara S, et al. Reverse redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial infarction. J Nucl Med 1996;37:1289-94.
20. Fujiwara S, Takeishi Y, Atsumi H, et al. Prediction of functional recovery in acute myocardial infarction: comparison between sestamibi reverse redistribution and sestamibi/BMIPP mismatch. J Nucl Cardiol 1998;5:119-27.
21. Ayalew A, Marie PY, Menu P, et al. A comparison of the overall first-pass kinetics of thallium-201 and technetium-99m MIBI in normoxic and low-flow ischaemic myocardium. Eur J Nucl Med 2000;27:1632-40
22. Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R. Washout and redistribution between immediate and two-hour myocardial images using technetium-99m sestamibi. Eur J Nucl Med 1995;22:49-55.
23. Meerdink DJ, Leppo JA. Myocardial transport of hexakis (2-methoxyisobutyl isonitrile) and thallium before and after coronary reperfusion. Circulation Research 1990;66:1738-46.
24. Ayalew A, Marie PY, Menu P, et al. 201 Tl and 99m Tc-MIBI retention in an isolated heart model of low-flow ischemia and stunning: Evidence of negligible impact of myocyte metabolism on tracer kinetics. J Nucl Med 2002;43:566-74.
25. Takahashi N, Reinhardt CP, Marcel R, Leppo JA. Myocardial uptake of 99m Tc-tetrofosmin, Sestamibi, and 201 Tl in a model of acute coronary reperfusion. Circulation 1996;94:2605-13.

Data that we have published at peer reviewed conferences or peer reviewed medical journals and websites:

References for FH Washout include (all peer reviewed):

- 1.) Presentation at the C-Care Conference in Berlin, July 2008
- 2.) Presentation at the 9th International Nuclear Cardiology Conference in Barcelona, May 2009
- 3.) Request for my presentation at the 8th International Congress on Coronary Artery Disease in Prague, October 2009
- 4.) Publication of FH Washout on the American Society of Nuclear Cardiology Website under Educational Cases.
- 5.) Publication of FH Washout in the January 2009 Imaging Update (official ASNC newsletter) of the American Society of Nuclear Cardiology
- 6.) Publication in the following Textbook, Spring 2009: Fleming RM, Harrington GM, Baqir R. Using Multiple Images Post-stress to Enhance Diagnostic Accuracy of Myocardial Perfusion Imaging: The Clinical Importance of Determining Washin & Washout Indicates a Parabolic Function Between Coronary Perfusion (Blood Flow) and Cellular ("Uptake/Release) Function. (submitted by "invitation only" to Nova Science March 2008, Heart Disease in Men.)
- 7.) Publication in the next edition of the Journal of the Methodist DeBakey Heart & Vascular Center.
- 8.) Several other publications are under review.

Finally, I am attaching a copy of the upcoming peer-review publication in the Journal of the Methodist DeBakey Heart & Vascular Center. (This is currently embargoed and not for release to anyone until published).

Yours,

Dr. Richard M. Fleming
Re: not superglue

From: **Mike Hansen** (Mike_Hansen@fd.org)
Sent: Mon 2/23/09 2:45 PM
To: RM Fleming (rmfmd7@hotmail.com)
you beat me to the punch. Thank you.

RM Fleming
<rmfmd7@hotmail.c
om>

02/23/2009 04:41
PM

Mike Hansen PD corrected
<mike_hansen@fd.org>

To

cc

Subject

not superglue

Mike,

Here you go. There are other articles which I sent you from June 2007 ->
Feb 2008 which are also important. I will look for these.

- 1) Blumgart and Yens 1926, publish paper on "Circulation Time."
- 2) Maublant JC, Gachon P, Moins N. Hexakis (2-methoxy isobutylisonitrile) technetium-99m and thallium-201 chloride: uptake and release in cultured myocardial cells. J Nucl Med 1988; 29(1):48-54. Proves washout of sestamibi in non-ischemic tissue is 28 minutes (enough for 2 washouts in 55 minutes).
- 3) Li Q-S, Solot G, Frank TL, Wagner HN, and Becker LC. Myocardial redistribution of technetium-99m-methoxyisobutyl isonitrile (sestamibi), J Nucl Med 1990;31:1069-1075. Proves that sestamibi washes out (redistributes) even faster than the 28 minutes noted by Maublant, when ischemia is present.
- 4) Crane P, Laliberte R, Heminway S, Thoolen M, Orlandi C. Effect of mitochondrial viability and metabolism on technetium-99m-sestamibi myocardial retention. Eur J Nucl Med 1993;20:20-25. A study paid for by Dupont who owned sestamibi proves that the reason sestamibi washes out sooner in ischemic tissue than non-ischemic tissue, is that ischemic tissue has mitochondrial calcium overload which results in faster washout of sestamibi.

All these studies show sestamibi doesn't go in and stick like superglue; but, rather washes out in normal tissue in 28 minutes and even faster in regions with coronary artery disease. The Blumgart paper was the original

nuclear cardiology paper showing serial collection of data was the way to go!

These are the 28 other papers referenced. They show the importance of looking at washout under different conditions. If sestamibi washes out with cancer, it will washout of other tissue. It is the mitochondria present in cancers, ischemic tissue and normal tissue which the sestamibi washes in and out of!!!

1. Pace L, Catalano L, Del Vecchio S, et al. Washout of [99mTc] sestamibi in predicting response to chemotherapy in patients with multiple myeloma. *Q J Nucl Med Mol Imaging* 2005;49:281-5.
2. Hurwitz GA, Ghali SK, Husni M, et al. Pulmonary uptake of Technetium-99m-Sestamibi induced by dipyridamole-based stress or exercise. *J Nucl Med* 1998;39:339-45.
3. Hurwitz GA, Fox SP, Driedger AA, Willems C, Powe JE. Pulmonary uptake of sestamibi on early post-stress images: angiographic relationships, incidence and kinetics. *Nucl Med Commun* 1993;14:15-22.
4. Saha M, Forrest TF, Brown KA. Lung uptake of technetium-99m-sestamibi: relation to clinical, exercise, hemodynamic, and left ventricular function variables. *J Nucl Cardiol* 1994;1:52-6.
5. Giubbini R, Bampini R, Milan E, et al. Evaluation of technetium-99m-sestamibi lung uptake: correlation with left ventricular function. *J Nucl Med* 1995;36:58-63.
6. Sugiura T, Takase H, Toriyama T, et al. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.
7. Kumita S, Seino Y, Cho K, et al. Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison with normal control. *Ann Nucl Med* 2002;16:237-42.
8. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. *J Nucl Cardiol* 2007;14:215-20.
9. Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.
10. Ikawa M, Kawai Y, Arakawa K, et al. Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of 99mTc-MIBI washout and 123I-BMIPP/99mTc-MIBI mismatch. *Mitochondrion* 2007;7:164-70.
11. Meissner K, Sperker B, Karsten C, et al. Expression and localization of P-glycoprotein in Human Heart: Effects of Cardiomyopathy. *J Histochem Cytochem* 2002;50:1351-6.
12. Ono S, Yamaguchi H, Takayama S, Kurabe A, Heito T. Rest delayed images on 99mTc-MIBI myocardial SPECT as a noninvasive screen for the diagnosis of vasospastic angina pectoris. *Kaku Igaku* 2002;39:117-24.
13. Ono S, Yakeishi Y, Yamaguchi H, et al. Enhanced regional washout of technetium-99m-sestamibi in patients with coronary spastic angina. *Ann Nucl Med* 2003;17:393-8.
14. Fukushima K, Momose M, Kondo C, et al. Myocardial kinetics of (201) Thallium, (99m) Tc-tetrofosmin, and (99m) Tc-sestamibi in an acute ischemia-reperfusion model using isolated rat heart. *Ann Nucl Med* 2007;21:267-73.
15. VanBrocklin HF, Hanrahan SM, Enas JD, et al. Mitochondrial avid radioprobes. Preparation and evaluation of 7'(Z)-[125I]iodorotenone and 7'(Z)-[125I]iodorotenol. *Nucl Med Biol* 2007;34:109-16.

16. Tanaka R, Nakamura T, Chiba S, et al. Clinical implication of reverse redistribution on 99mTc-sestamibi images for evaluating ischemic heart disease. *Ann Nucl Med* 2006;20:349-56.
17. Liu Z, Johnson G 3rd, Beju D, Okada RD. Detection of myocardial viability in ischemic-reperfused rat hearts by Tc-99m sestamibi kinetics. *J Nucl Cardiol* 2001;8:677-86.
18. Shin WJ, Miller K, Stipp V, Mazour S. Reverse redistribution on dynamic exercise and dipyridamole stress technetium-99m-MIBI myocardial SPECT. *J Nucl Med* 1995;36:2053-5
19. Takeishi Y, Sukekawa H, Fujiwara S, et al. Reverse redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial infarction. *J Nucl Med* 1996;37:1289-94.
20. Fujiwara S, Takeishi Y, Atsumi H, et al. Prediction of functional recovery in acute myocardial infarction: comparison between sestamibi reverse redistribution and sestamibi/BMIPP mismatch. *J Nucl Cardiol* 1998;5:119-27.
21. Ayalew A, Marie PY, Menu P, et al. A comparison of the overall first-pass kinetics of thallium-201 and technetium-99m MIBI in normoxic and low-flow ischaemic myocardium. *Eur J Nucl Med* 2000;27:1632-40
22. Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R. Washout and redistribution between immediate and two-hour myocardial images using technetium-99m sestamibi. *Eur J Nucl Med* 1995;22:49-55.
23. Meerdink DJ, Leppo JA. Myocardial transport of hexakis (2-methoxyisobutyl isonitrile) and thallium before and after coronary reperfusion. *Circulation Research* 1990;66:1738-46.
24. Ayalew A, Marie PY, Menu P, et al. 201 Tl and 99m Tc-MIBI retention in an isolated heart model of low-flow ischemia and stunning: Evidence of negligible impact of myocyte metabolism on tracer kinetics. *J Nucl Med* 2002;43:566-74.
25. Takahashi N, Reinhardt CP, Marcel R, Leppo JA. Myocardial uptake of 99m Tc-tetrofosmin, Sestamibi, and 201 Tl in a model of acute coronary reperfusion. *Circulation* 1996;94:2605-13.

Dr. Fleming

FW: Use of two SPECT images with sestamibi - references for court - complete set

From:

RM Fleming (rmfmd7@hotmail.com)

Sent: Mon 2/23/09 2:49 PM

To: Mike Hansen PD corrected (mike_hansen@fd.org); rmfmd7@hotmail.com

> Date: Mon, 27 Aug 2007 23:36:33 -0500

> From: gordon.harrington@uni.edu

> To: rmfmd7@hotmail.com

> Subject: Use of two SPECT images with sestamibi - references for court - complete set

>

> Richard,

>

> To organize dribs and drabs, here in one place as one complete set for

> the case are:

> 1. two full text research articles supporting diagnostic uses of a

> second image (attachments ANM*),

> 2. five additional abstracts (1-5 below) supporting diagnostic use of a

> second image,

> 3 four additional abstracts (6-9) on sestamibi kinetics (changes over time),

> 4 one full text article with graphics of sestamibi kinetics (attachment

> 272).

>

> A. SECOND IMAGE USE

>

> 1.*** Diagnostic use of second image - full text not available in my

> library ***

> J Nucl Cardiol. 2007 Apr;14(2):215-20. Click here to read Links

> A novel clinical indicator using Tc-99m sestamibi for evaluating

> cardiac mitochondrial function in patients with cardiomyopathies.

> Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M.

>

> Department of Cardiovascular and Respiratory Medicine, Shiga

> University of Medical Science, Shiga, Japan. smatsuo@belle.shiga-med.ac.jp

>

> BACKGROUND: Technetium 99m sestamibi (MIBI) is a technetium-labeled

> myocardial perfusion agent that is taken up by the myocardial cell in

> proportion to myocardial regional blood flow and remains fixed in the

> myocardial cell over a long period of time. Previous studies have

> suggested that MIBI shows very slow myocardial clearance after its

> initial uptake in an animal model, which is related to mitochondrial

> function. This study was designed to test the hypothesis that MIBI

> washout can be used to evaluate the severity of congestive heart failure

> in comparison to other clinical parameters in patients with

> cardiomyopathies. METHODS AND RESULTS: After administration of MIBI, 61

> patients with nonischemic congestive heart failure (49 with dilated

> cardiomyopathy and 12 with other cardiomyopathies) and 7 normal control

> subjects were examined by electrocardiography-gated myocardial perfusion

> single photon emission computed tomography and planar data acquisition

> in the early and delayed phases (interval of 3 hours). Myocardial MIBI

> washout rates were calculated from the early and delayed planar images.

> Left ventricular function (systolic and diastolic) was analyzed by use

> of QGS data. Plasma levels of B-type natriuretic peptide and iodine 123

> metaiodobenzylguanidine (MIBG) parameters were also measured. Patients

> were followed up for a mean of 12 months (range, 1-19 months). As the
 > severity of the New York Heart Association (NYHA) functional class
 > advanced, the washout rate of MIBI increased ($21.6\% \pm 2.4\%$ in those with
 > NYHA class I [$n = 23$], $28\% \pm 4\%$ in those with NYHA class II [$n = 27$],
 > and $35\% \pm 5\%$ in those with NYHA class III [$n = 10$]; $P < .05$, analysis of
 > variance). The washout rate of MIBI was positively correlated with the
 > level of B-type natriuretic peptide ($r = 0.31$, $P < .05$), end-diastolic
 > volume ($r = 0.396$, $P < .01$), and end-systolic volume ($r = 0.496$, $P <$
 > $.01$) and was negatively correlated with left ventricular ejection
 > fraction ($r = 0.523$, $P < .01$), peak filling rate ($r = 0.444$, $P < .01$),
 > and first-third ejection fraction ($r = 0.414$, $P < .01$). The parameters
 > of MIBG scintigraphy were calculated as the heart-mediastinum count
 > ratio (1.9 ± 3) and washout rate ($38\% \pm 4\%$). We found a significant
 > relationship between the washout rate of MIBI and the heart-mediastinum
 > count ratio of MIBG ($r = 0.51$, $P < .01$). Patients with a higher washout
 > rate of MIBI had a higher cardiac event rate ($> \text{or} \approx 28\%$) than those with
 > a lower washout rate ($< 28\%$) ($P < .05$). CONCLUSIONS: The myocardial
 > washout rate of MIBI is thought to be a novel marker for the diagnosis
 > of myocardial damage or dysfunction, providing prognostic information in
 > patients with congestive heart failure.

> PMID: 17386384 [PubMed - indexed for MEDLINE]

> 2.*** Diagnostic use of second image - full text not available in my
 > library ***

> J Nucl Cardiol. 1998 Mar-Apr;5(2):119-27. Related Articles, Links

> Click here to read

> Comment in:

> * J Nucl Cardiol. 1998 Mar-Apr;5(2):202-5.

> Prediction of functional recovery in acute myocardial infarction:

> comparison between sestamibi reverse redistribution and sestamibi/BMIPP
 > mismatch.

> Fujiwara S, Takeishi Y, Atsumi H, Yamaki M, Takahashi N, Yamaoka M,
 > Tojo T, Tomoike H.

> First Department of Internal Medicine, Yamagata University School of
 > Medicine, Iida-Nishi, Japan. sfujiwar@med.id.yamagata-u.ac.jp

> BACKGROUND: It has been known that Tc 99m sestamibi/iodine I23
 > betamethyl iodophenylpentadecanoic (I23I-BMIPP) (sestamibi/BMIPP)
 > mismatch is an indicator of viable myocardium in acute myocardial
 > infarction (AMI). We have reported that reverse redistribution of
 > sestamibi in AMI indicates the patency of infarct-related artery and a
 > preserved left ventricular function in the chronic stage. In this study
 > we investigated the relationship between reverse redistribution of
 > sestamibi and sestamibi/BMIPP mismatch in patients with AMI. METHODS:
 > Twenty-three patients with AMI who received direct percutaneous
 > transluminal coronary angioplasty underwent both BMIPP and sestamibi
 > SPECT within 2 weeks after onset. Sestamibi images were obtained 1 hour
 > (early) and 3 hours (delayed) after injection of sestamibi. BMIPP
 > imaging was carried out 30 minutes after injection. The left ventricle
 > was divided into 17 segments, and regional myocardial uptakes of the

> tracers in each segment were scored from 0 (normal) to 3 (no activity).
 > A reverse redistribution pattern was defined as an increase of ≥ 1
 > in the regional score at the delayed images. More reduced BMIPP uptake
 > than sestamibi uptake in each segment was determined as sestamibi/BMIPP
 > mismatch. Contrast left ventriculography was performed soon after
 > revascularization and repeated 1 month later. RESULTS: Of 15 patients
 > with sestamibi reverse redistribution, sestamibi/BMIPP mismatch was
 > observed in 14 patients (93%), whereas mismatch was seen in only one of
 > seven patients (14%) without reverse redistribution ($p < 0.01$). In
 > patients with sestamibi reverse redistribution, regional scores of BMIPP
 > agreed with those of early and delayed images of sestamibi in 51
 > segments (46%) and in 92 segments (83%), respectively. In the chronic
 > stage, both regional wall motion and left ventricular ejection fraction
 > improved in patients with sestamibi reverse redistribution (wall motion
 > score: 6.7 ± 2.4 vs 2.7 ± 2.1 , $p < 0.01$; ejection fraction: $56\% \pm 7\%$ vs
 > $64\% \pm 8\%$, $p < 0.01$), but not in those without reverse redistribution.
 > CONCLUSION: Both reverse redistribution of sestamibi and sestamibi/BMIPP
 > mismatch reflect the recovery of left ventricular function and thus
 > imply myocardial viability in AMI. Because the presence of reverse
 > redistribution of sestamibi agreed with that of sestamibi/BMIPP
 > mismatch, additional BMIPP images can be replaced by the delayed images
 > after a single injection of sestamibi.
 >
 > Publication Types:
 >
 > * Comparative Study
 > * Research Support, Non-U.S. Gov't
 >
 >
 > PMID: 9588663 [PubMed - indexed for MEDLINE] .
 >
 > 3. *** Diagnostic use of second image - full text not available in my
 > library ***
 > J Nucl Cardiol. 2006 Jan-Feb;13(1):64-8. Related Articles, Links
 > Click here to read
 > Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for
 > evaluating congestive heart failure.
 >
 > Sugiyama T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y.
 >
 > Department of Internal Medicine, Enshu General Hospital, Hamamatsu,
 > and Department of Internal Medicine and Molecular Science, Graduate
 > School of Medical Sciences, Nagoya City University, Japan.
 >
 > BACKGROUND: Evidence is accumulating that technetium 99m
 > methoxyisobutylisonitrile (MIBI) is not retained in the impaired
 > myocardium. The purpose of this study was to determine whether the
 > severity of congestive heart failure (CHF) can be evaluated by use of
 > the washout rate (WR) of MIBI. METHODS AND RESULTS: Seventeen patients
 > with CHF and ten healthy volunteers were enrolled in this study. MIBI
 > and iodine 123 metaiodobenzylguanidine (MIBG) scintigraphy techniques
 > were performed, and the WR was calculated. The blood was also sampled
 > for the measurement of levels of brain natriuretic peptide, which is a
 > powerful predictor of the severity of CHF. The WR of MIBI was higher in
 > CHF patients ($31.2\% \pm 6.3\%$) than in healthy volunteers ($25.2\% \pm 4.7\%$)
 > ($P < .05$). There were positive correlations between the WR of MIBI and

> brain natriuretic peptide levels ($r=0.723$, $P<.0001$) and a negative
 > correlation between the WR of MIBI and the left ventricular ejection
 > fraction ($r=-0.545$, $P<.01$). The WR of MIBI was correlated with that of
 > MIBG ($r=0.603$, $P<.01$). CONCLUSIONS: MIBI scintigraphy is useful in
 > evaluating the severity of congestive heart failure.
 >
 > Publication Types:
 >
 > * Comparative Study
 > * Controlled Clinical Trial
 >
 >
 > PMID: 16464718 [PubMed - indexed for MEDLINE]
 >
 > 4. *** Diagnostic use of second image - English full text not available ***
 > Kaku Igaku. 2002 May;39(2):117-24. Related Articles, Links
 >
 > [Rest delayed images on 99mTc-MIBI myocardial SPECT as a noninvasive
 > screen for the diagnosis of vasospastic angina pectoris]
 >
 > [Article in Japanese]
 >
 > Ono S, Yamaguchi H, Takayama S, Kurabe A, Heito T.
 >
 > Department of Radiology, Yamagata Prefectural Shinjo Hospital.
 >
 > Diagnostic usefulness of 99mTc-MIBI myocardial SPECT at rest was
 > examined in 39 cases of coronary vasospastic angina pectoris who were
 > diagnosed by a positive reaction to ergonovine provocation. SPECT was
 > performed 45 minutes (early image) and 3 hours (delayed image) after the
 > intravenous injection of approximately 600 MBq of MIBI. Decrease in
 > accumulation was ranked by four defect scores (0: normal; 1: slight
 > decrease; 2: moderate decrease; 3: severe decrease) and the total defect
 > score was evaluated semiquantitatively. The washout rate between the
 > normal area and the spasm area was also evaluated quantitatively using
 > bull's eye. As a result, 15 cases (15/39; 38.4%) showed decreased
 > accumulation in the early image and 27 cases (27/39; 69.2%) showed
 > decreased accumulation in the delayed image. All of the cases which
 > showed decreased accumulation in the early image had decreased
 > accumulation in the delayed image as well. In 6 cases (6/34; 17.6%)
 > showed ST wave changes during exercise ECG and 16 cases (16/34; 47%)
 > showed decreased accumulation in the exercise myocardial SPECT. The
 > washout rate of MIBI in the decreased accumulation area was
 > significantly higher than that of the normal area. Of 32 ergonovine
 > induced vasospastic area, 23 areas (72%) exhibited decreased
 > accumulation in the delayed image for the same area. Decreased
 > accumulation in the delayed image in MIBI was due to the enhanced
 > washout, which, in turn, indicated declined retention of MIBI by
 > mitochondrial membrane. In coronary vasospastic angina pectoris, spasm
 > induced ischemia was thought to have an effect on the mitochondria. This
 > study suggested that even with a normal exercise ECG and exercise
 > myocardial SPECT, there's a strong possibility of coronary vasospastic
 > angina pectoris if a decreased accumulation was found in the delayed
 > image in the MIBI myocardial SPECT at rest. Hence, in diagnosing
 > coronary vasospastic angina pectoris, the delayed image in the MIBI
 > myocardial SPECT at rest was believed to be useful.

>
> Publication Types:
>
> * English Abstract
>
>
> PMID: 12058420 [PubMed - indexed for MEDLINE]
>
> 5. *** Diagnostic use of second image - full text not available in my
> library ***
> *J Nucl Cardiol. <javascript:AL_get(this, 'jour', 'J Nucl Cardiol.*)>
> 2001 Nov-Dec;8(6):677-86. Related Articles
>
<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pub
med&LinkReadableName=Related%20Articles&IdsFromResult=11725264&ordinalpos=26&itool=EntrezSystem2.
PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
>
> Links <javascript:PopUpMenu2_Set(Menu11725264)*>
>
> Click here to read
>
> <http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?PrId=3048&itool=Abstract-
def&uid=11725264&db=pubmed&url=http://linkinghub.elsevier.com/retrieve/pii/S1071-3581%2801%2954260-9>
>
> *Detection of myocardial viability in ischemic-reperfused rat hearts
> by Tc-99m sestamibi kinetics.*
>
> *Liu Z*
>
>
<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Liu%20Z%22%5BAuthor%5D
&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
> *Johnson G 3rd*
>
>
<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Johnson%20G%203rd%22%5B
Author%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
> *Beju D*
>
>
<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Beju%20D%22%5BAuthor%5
D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
> *Okada RD*
>
>
<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Okada%20RD%22%5BAuthor
%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>.
>
> William K. Warren Medical Research Institute of the University of
> Oklahoma Health Sciences Center, Tulsa , USA. zliu@u.arizona.edu
>
> BACKGROUND: The purpose of this study was to evaluate technetium 99m
> sestamibi (MIBI) kinetics in assessing myocardial viability in
> hearts subjected to different ischemia-reperfusion treatments,
> resulting in graded severity of injury. METHODS AND RESULTS: Sixteen
> isolated Krebs-Henseleit-perfused rat hearts were divided into 3

> groups: control (flow, 12 mL/min; n = 5), ischemic-reperfused with
 > glucose (IR+G, n = 6), and ischemic-reperfused without glucose
 > (IR-G, n = 5). MIBI (11.1 mBq [300 microCi]) was infused for 60
 > minutes (uptake), followed by a 60-minute clearance. MIBI uptake
 > (percent injected dose per gram) was significantly decreased in the
 > IR+G (2.07 ± 0.31) and IR-G groups (2.03 ± 0.23 ; P = not
 > significant with IR+G) compared with the control group ($3.06 \pm$
 > 0.25 , $P < .05$). Fractional washout of MIBI was more rapid in the IR-G
 > group ($72.7\% \pm 3.9\%$, $P < .05$) than in the control ($21.9\% \pm 1.9\%$)
 > and IR+G groups ($20.3\% \pm 1.7\%$). End retention (percent injected
 > dose per gram) of MIBI in the IR-G (0.60 ± 0.12) and IR+G groups
 > (1.60 ± 0.18) was significantly less than in the control group
 > (2.30 ± 0.11 , $P < .05$), respectively. The retention in the IR-G
 > group was less than in the IR+G group ($P < .05$). Creatine kinase
 > assay, triphenyltetrazolium chloride staining, and transmission
 > electron microscopy analysis demonstrated more serious myocardial
 > damage in the IR-G group than in the IR+G group. End MIBI activity
 > was highly correlated with myocardial viability determined by
 > triphenyltetrazolium chloride staining ($r = 0.94$; $P < .05$) and
 > creatine kinase assay ($r = -0.86$; $P < .05$). CONCLUSIONS: Clearance of
 > Tc-99m sestamibi is sensitive to metabolic states and may be used
 > for assessment of ongoing myocardial damage.
 >
 > PMID: 11725264 [PubMed - indexed for MEDLINE]
 >
 > B. SESTAMIBI KINETICS
 >
 > 6. *** Rat study of sestamibi kinetics - full text not available in my
 > library ***
 > J Nucl Cardiol. 2001 Nov-Dec;8(6):677-86. Related Articles, Links
 > Click here to read
 > Detection of myocardial viability in ischemic-reperfused rat hearts
 > by Tc-99m sestamibi kinetics.
 >
 > Liu Z, Johnson G 3rd, Beju D, Okada RD.
 >
 > William K. Warren Medical Research Institute of the University of
 > Oklahoma Health Sciences Center, Tulsa , USA. zliu@u.arizona.edu
 >
 > BACKGROUND: The purpose of this study was to evaluate technetium 99m
 > sestamibi (MIBI) kinetics in assessing myocardial viability in hearts
 > subjected to different ischemia-reperfusion treatments, resulting in
 > graded severity of injury. METHODS AND RESULTS: Sixteen isolated
 > Krebs-Henseleit-perfused rat hearts were divided into 3 groups: control
 > (flow, 12 mL/min; n = 5), ischemic-reperfused with glucose (IR+G, n =
 > 6), and ischemic-reperfused without glucose (IR-G, n = 5). MIBI (11.1
 > mBq [300 microCi]) was infused for 60 minutes (uptake), followed by a
 > 60-minute clearance. MIBI uptake (percent injected dose per gram) was
 > significantly decreased in the IR+G (2.07 ± 0.31) and IR-G groups (2.03
 > ± 0.23 ; P = not significant with IR+G) compared with the control group
 > (3.06 ± 0.25 , $P < .05$). Fractional washout of MIBI was more rapid in the
 > IR-G group ($72.7\% \pm 3.9\%$, $P < .05$) than in the control ($21.9\% \pm 1.9\%$) and
 > IR+G groups ($20.3\% \pm 1.7\%$). End retention (percent injected dose per
 > gram) of MIBI in the IR-G (0.60 ± 0.12) and IR+G groups (1.60 ± 0.18)
 > was significantly less than in the control group (2.30 ± 0.11 , $P < .05$),
 > respectively. The retention in the IR-G group was less than in the IR+G

> group ($P < .05$). Creatine kinase assay, triphenyltetrazolium chloride staining, and transmission electron microscopy analysis demonstrated more serious myocardial damage in the IR-G group than in the IR+G group. > End MIBI activity was highly correlated with myocardial viability > determined by triphenyltetrazolium chloride staining ($r = 0.94$; $P < .05$) > and creatine kinase assay ($r = -0.86$; $P < .05$). CONCLUSIONS: Clearance of > Tc-99m sestamibi is sensitive to metabolic states and may be used for > assessment of ongoing myocardial damage.

>

> PMID: 11725264 [PubMed - indexed for MEDLINE]

>

> 7. *** Sestamibi kinetics - full text not available in my library***

> Eur J Nucl Med. 2000 Nov;27(11):1632-40. Related Articles, Links

> Click here to read

> A comparison of the overall first-pass kinetics of thallium-201 and > technetium-99m MIBI in normoxic and low-flow ischaemic myocardium.

>

> Ayalew A, Marie PY, Menu P, Mertes PM, Hassan N, Danchin N, Olivier > P, Karcher G, Bertrand A.

>

> Department of Nuclear Medicine, UPRES EA 2403, CHU-Nancy, France.

>

> The specific impact of ischaemia on the myocardial kinetics of > thallium-201 and technetium-99m 2-methoxy-2-isobutylisonitrile (MIBI) > remains a matter of debate. Using an isolated heart model perfused with > red blood cell-enhanced perfusate, we compared the overall first-pass > kinetics of 201Tl and MIBI under haemodynamically stable conditions of > low-flow ischaemia (> 50% reduction in normal coronary flow and a > = > 20 mmHg fall in systolic contraction pressure, $n = 10$) and normoxia ($n =$ > 11). For both 201Tl and MIBI, we found that under ischaemic conditions > (as compared with normoxia) there was a higher initial net extraction > fraction (201Tl: 0.78 ± 0.03 vs 0.72 ± 0.06 , $P = 0.006$; MIBI: $0.49 \pm$ > 0.10 vs 0.39 ± 0.11 , $P = 0.03$), a lower clearance rate in the 30 min > following extraction (% decrease in cardiac uptake: 201Tl: 30 ± 12 vs 47 > ± 14 , $P = 0.02$; MIBI: 5 ± 5 vs 13 ± 11 , $P = 0.02$) and a higher retention > fraction at 30 min (201Tl: 0.54 ± 0.10 vs 0.39 ± 0.12 , $P = 0.004$; MIBI: > 0.46 ± 0.08 vs 0.33 ± 0.12 , $P = 0.01$). Multivariate analyses, however, > revealed that all myocardial kinetic parameters of both tracers were > dependent only on coronary flow rates, without any additional > significant impact of the presence of ischaemia or states of > contractility or oxidative metabolism. We conclude that the myocardial > fractional retention of both 201Tl and MIBI is strongly correlated with > the decrease in coronary flow during ischaemia. This inverse > relationship with coronary flow derives from both the flow-dependent > increase in the initial myocardial extraction and the decrease in the > subsequent myocardial washout of the tracers.

>

> Publication Types:

>

> * Comparative Study

> * Research Support, Non-U.S. Gov't

>

>

> PMID: 11105819 [PubMed - indexed for MEDLINE]

>

> 8. *** Sestamibi kinetics - full text not available in my library ***

> Eur J Nucl Med. 1995 Jan;22(1):49-55. Related Articles, Links
>
> Washout and redistribution between immediate and two-hour myocardial
> images using technetium-99m sestamibi.
>
> Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R.
>
> Universitätsklinikum Rudolf Virchow, Freie Universität Berlin, Germany.
>
> The aim of this study was to assess whether a clinically relevant
> change in myocardial sestamibi activity could be documented within the
> first 120 min following injection (p.i.). In 17 patients planar anterior
> imaging of the heart was performed 5 min and 120 min p.i. During this
> time interval, mean decay-corrected myocardial activity declined to
> $77.9\% \pm 9.7\%$ after stress and to $85.7\% \pm 7.9\%$ after injection at rest (P
> < 0.05). In 19 patients with angiographically documented coronary artery
> disease, single-photon emission tomography was performed 5 min and 120
> min after injection at maximum stress. For analysis, sestamibi activity
> was scored semiquantitatively in six left ventricular segments.
> Furthermore, sestamibi uptake was assessed quantitatively using a
> circumferential profile method. In 35 of 114 segments the score improved
> within 120 min p.i. (early fill-in); in these segments relative
> sestamibi activity rose from $69.9\% \pm 22.5\%$ to $74.5\% \pm 20.8\%$ ($P < 0.01$).
> In five patients this early fill-in was the only sign of
> exercise-induced hypoperfusion. In 7 of 114 segments the score
> deteriorated 120 min p.i. (early tracer washout); in these segments
> relative sestamibi activity declined from $85.6\% \pm 9.9\%$ to $80.1\% \pm 10.7\%$
> ($P < 0.02$). In three of four patients with early tracer washout the
> corresponding coronary artery was significantly narrowed. In conclusion,
> a global myocardial sestamibi washout was registered within the first
> 120 min after injection. A fill-in of initial defects as well as an
> early tracer loss could be detected in a relevant number of patients
> with chronic coronary artery disease during the first 2 h p.i.(ABSTRACT
> TRUNCATED AT 250 WORDS)
>
> Publication Types:
>
> * Comparative Study
>
>
> PMID: 7698155 [PubMed - indexed for MEDLINE]
>
>
> 9. ***Rat study of sestamibi kinetics - full text not yet available from
> publisher***
> Ann Nucl Med. 2007 Jul;21(5):267-73. Epub 2007 Jul 25. Related
> Articles, Links
> Click here to read
> Myocardial kinetics of (201)Thallium, (99m)Tc-tetrofosmin, and
> (99m)Tc-sestamibi in an acute ischemia-reperfusion model using isolated
> rat heart.
>
> Fukushima K, Momose M, Kondo C, Kusakabe K, Kasanuki H.
>
> Department of Cardiology, Tokyo Women's Medical University, Tokyo,
> Japan.

>
 > OBJECTIVE: (201)Thallium (TL), (99m)Tc-tetrofosmin (TF), and
 > (99m)Tc-sestamibi (MIBI) are extensively used as myocardial perfusion
 > agents. The objective of the present study was to evaluate their
 > kinetics under acute ischemia-reperfusion. METHODS: Isolated rat hearts,
 > perfused by the Langendorff method at a constant flow rate of 10 ml/min,
 > were allotted to normal control, mild ischemia, and severe ischemia
 > groups, in which 20-min tracer wash-in was conducted followed by a
 > 25-min tracer washout. No-flow ischemia (15 min for mild ischemia
 > groups; 30 min for severe ischemia groups) was induced before conducting
 > wash-in and washout in the ischemia groups. Whole-heart radioactivity
 > was determined with an external gamma detector. Myocardial flow rate (K
 > (1), ml/min) and clearance rate (k (2), min⁻¹) were calculated.
 > RESULTS: K (1TL), K (1TF), and K (1MIBI) decreased according to the
 > severity of ischemia (K (1TL) 5.32 ± 0.53, 4.76 ± 0.70, and 1.44 ± 0.59;
 > K (1TF) 3.80 ± 0.70, 2.73 ± 0.99, and 1.09 ± 0.45; and K (1MIBI) 3.45 ±
 > 1.10, 2.15 ± 0.82, and 1.05 ± 0.13, in the normal control, mild, and
 > severe ischemia groups, respectively). K (1) was significantly higher
 > for TL than for the (99m)Tc tracers (P < 0.05), but the (99m)Tc tracers
 > had equivalent K (1) values. k (2TL) increased significantly (P < 0.05)
 > in the ischemia groups (k (2TL) 0.062 ± 0.013, 0.11 ± 0.045, and 0.12 ±
 > 0.035), but showed no significant difference between the ischemia
 > groups. k (2MIBI) and k (2TF) were significantly (P < 0.05) lower than k
 > (2TL) and increased significantly (P < 0.05) in the severe ischemia
 > group (k (2TF) 0.0056 ± 0.0022, 0.0037 ± 0.0015, and 0.024 ± 0.015; and
 > k (2MIBI) 0.00072 ± 0.0011, 0.00038 ± 0.00076, and 0.042 ± 0.034). k
 > (2MIBI) was significantly (P < 0.05) lower than k (2TF) in the normal
 > control and mild ischemia groups. CONCLUSIONS: Tracer extraction was
 > higher for TL than for the (99m)Tc tracers and all tracers decreased
 > according to the severity of ischemia-reperfusion in the three tracer
 > groups. The clearance kinetics of not only MIBI but also TF is possibly
 > useful for the evaluation of the severity of ischemia, and the
 > Langendorff method and a methodological approach by continuous
 > determinations of radioactivity may serve for the quantitative analysis
 > of tracer kinetic profiles.

>
 > PMID: 17634844 [PubMed - in process]

>
 > —
 > Gordon M. Harrington, Professor Emeritus
 > University of Northern Iowa
 > 3720 Village Place, #6308
 > Waterloo, Iowa 50702-5848
 > Phone: 319-291-8535 Fax: 319-291-8491
 > gordon.harrington@uni.edu dryfly@aya.yale.edu

FW: Use of two SPECT images with sestamibi - references for court - complete set

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 2/23/09 2:49 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org); Richard Fleming (rmfmd7@hotmail.com)
3 attachments
[ANM20-5-0...pdf](#) (54.9 KB), [ANM16-4-0...pdf](#) (38.9 KB), [272.pdf](#) (139.5 KB)

> Date: Mon, 27 Aug 2007 23:36:33 -0500
> From: gordon.harrington@uni.edu
> To: rmfmd7@hotmail.com
> Subject: Use of two SPECT images with sestamibi - references for court - complete set
>
> Richard,
>
> To organize dribs and drabs, here in one place as one complete set for
> the case are:
> 1. two full text research articles supporting diagnostic uses of a
> second image (attachments ANM*),
> 2. five additional abstracts (1-5 below) supporting diagnostic use of a
> second image,
> 3 four additional abstracts (6-9) on sestamibi kinetics (changes over time),
> 4 one full text article with graphics of sestamibi kinetics (attachment
> 272).
> .
> A. SECOND IMAGE USE
>
> 1. *** Diagnostic use of second image - full text not available in my
> library ***
> J Nucl Cardiol. 2007 Apr;14(2):215-20. Click here to read Links
> A novel clinical indicator using Tc-99m sestamibi for evaluating
> cardiac mitochondrial function in patients with cardiomyopathies.
> Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M.
>
> Department of Cardiovascular and Respiratory Medicine, Shiga
> University of Medical Science, Shiga, Japan. smatsuo@belle.shiga-med.ac.jp
>
> BACKGROUND: Technetium 99m sestamibi (MIBI) is a technetium-labeled
> myocardial perfusion agent that is taken up by the myocardial cell in
> proportion to myocardial regional blood flow and remains fixed in the
> myocardial cell over a long period of time. Previous studies have
> suggested that MIBI shows very slow myocardial clearance after its
> initial uptake in an animal model, which is related to mitochondrial
> function. This study was designed to test the hypothesis that MIBI
> washout can be used to evaluate the severity of congestive heart failure
> in comparison to other clinical parameters in patients with
> cardiomyopathies. METHODS AND RESULTS: After administration of MIBI, 61
> patients with nonischemic congestive heart failure (49 with dilated
> cardiomyopathy and 12 with other cardiomyopathies) and 7 normal control
> subjects were examined by electrocardiography-gated myocardial perfusion
> single photon emission computed tomography and planar data acquisition
> in the early and delayed phases (interval of 3 hours). Myocardial MIBI
> washout rates were calculated from the early and delayed planar images.

> Left ventricular function (systolic and diastolic) was analyzed by use
> of QGS data. Plasma levels of B-type natriuretic peptide and iodine 123
> metaiodobenzylguanidine (MIBG) parameters were also measured. Patients
> were followed up for a mean of 12 months (range, 1-19 months). As the
> severity of the New York Heart Association (NYHA) functional class
> advanced, the washout rate of MIBI increased ($21.6\% \pm 2.4\%$ in those with
> NYHA class I [$n = 23$], $28\% \pm 4\%$ in those with NYHA class II [$n = 27$],
> and $35\% \pm 5\%$ in those with NYHA class III [$n = 10$]; $P < .05$, analysis of
> variance). The washout rate of MIBI was positively correlated with the
> level of B-type natriuretic peptide ($r = 0.31$, $P < .05$), end-diastolic
> volume ($r = 0.396$, $P < .01$), and end-systolic volume ($r = 0.496$, $P <$
> $.01$) and was negatively correlated with left ventricular ejection
> fraction ($r = 0.523$, $P < .01$), peak filling rate ($r = 0.444$, $P < .01$),
> and first-third ejection fraction ($r = 0.414$, $P < .01$). The parameters
> of MIBG scintigraphy were calculated as the heart-mediastinum count
> ratio (1.9 ± 3) and washout rate ($38\% \pm 4\%$). We found a significant
> relationship between the washout rate of MIBI and the heart-mediastinum
> count ratio of MIBG ($r = 0.51$, $P < .01$). Patients with a higher washout
> rate of MIBI had a higher cardiac event rate ($> \text{or} = 28\%$) than those with
> a lower washout rate ($< 28\%$) ($P < .05$). CONCLUSIONS: The myocardial
> washout rate of MIBI is thought to be a novel marker for the diagnosis
> of myocardial damage or dysfunction, providing prognostic information in
> patients with congestive heart failure.

>

> PMID: 17386384 [PubMed - indexed for MEDLINE]

>

> 2.*** Diagnostic use of second image - full text not available in my
> library ***

> J Nucl Cardiol. 1998 Mar-Apr;5(2):119-27. Related Articles, Links

> Click here to read

> Comment in:

>

> * J Nucl Cardiol. 1998 Mar-Apr;5(2):202-5.

>

>

> Prediction of functional recovery in acute myocardial infarction:
> comparison between sestamibi reverse redistribution and sestamibi/BMIPP
> mismatch.

>

> Fujiwara S, Takeishi Y, Atsumi H, Yamaki M, Takahashi N, Yamaoka M,
> Tojo T, Tomoike H.

>

> First Department of Internal Medicine, Yamagata University School of
> Medicine, Iida-Nishi, Japan. sfujiwar@med.id.yamagata-u.ac.jp

>

> BACKGROUND: It has been known that Tc 99m sestamibi/iodine 123
> betamethylodophenylpentadecanoic (123I-BMIPP) (sestamibi/BMIPP)
> mismatch is an indicator of viable myocardium in acute myocardial
> infarction (AMI). We have reported that reverse redistribution of
> sestamibi in AMI indicates the patency of infarct-related artery and a
> preserved left ventricular function in the chronic stage. In this study
> we investigated the relationship between reverse redistribution of
> sestamibi and sestamibi/BMIPP mismatch in patients with AMI. METHODS:

> Twenty-three patients with AMI who received direct percutaneous
> transluminal coronary angioplasty underwent both BMIPP and sestamibi
> SPECT within 2 weeks after onset. Sestamibi images were obtained 1 hour

> (early) and 3 hours (delayed) after injection of sestamibi. BMIPP
 > imaging was carried out 30 minutes after injection. The left ventricle
 > was divided into 17 segments, and regional myocardial uptakes of the
 > tracers in each segment were scored from 0 (normal) to 3 (no activity).
 > A reverse redistribution pattern was defined as an increase of > 1 or ≈ 1
 > in the regional score at the delayed images. More reduced BMIPP uptake
 > than sestamibi uptake in each segment was determined as sestamibi/BMIPP
 > mismatch. Contrast left ventriculography was performed soon after
 > revascularization and repeated 1 month later. RESULTS: Of 15 patients
 > with sestamibi reverse redistribution, sestamibi/BMIPP mismatch was
 > observed in 14 patients (93%), whereas mismatch was seen in only one of
 > seven patients (14%) without reverse redistribution ($p < 0.01$). In
 > patients with sestamibi reverse redistribution, regional scores of BMIPP
 > agreed with those of early and delayed images of sestamibi in 51
 > segments (46%) and in 92 segments (83%), respectively. In the chronic
 > stage, both regional wall motion and left ventricular ejection fraction
 > improved in patients with sestamibi reverse redistribution (wall motion
 > score: 6.7 ± 2.4 vs 2.7 ± 2.1 , $p < 0.01$; ejection fraction: $56\% \pm 7\%$ vs
 > $64\% \pm 8\%$, $p < 0.01$), but not in those without reverse redistribution.
 > CONCLUSION: Both reverse redistribution of sestamibi and sestamibi/BMIPP
 > mismatch reflect the recovery of left ventricular function and thus
 > imply myocardial viability in AMI. Because the presence of reverse
 > redistribution of sestamibi agreed with that of sestamibi/BMIPP
 > mismatch, additional BMIPP images can be replaced by the delayed images
 > after a single injection of sestamibi.
 >
 > Publication Types:
 >
 > * Comparative Study
 > * Research Support, Non-U.S. Gov't
 >
 >
 > PMID: 9588663 [PubMed - indexed for MEDLINE] .
 >
 > 3. *** Diagnostic use of second image - full text not available in my
 > library ***
 > J Nucl Cardiol. 2006 Jan-Feb;13(1):64-8. Related Articles, Links
 > Click here to read
 > Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for
 > evaluating congestive heart failure.
 >
 > Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y.
 >
 > Department of Internal Medicine, Enshu General Hospital, Hamamatsu,
 > and Department of Internal Medicine and Molecular Science, Graduate
 > School of Medical Sciences, Nagoya City University, Japan.
 >
 > BACKGROUND: Evidence is accumulating that technetium 99m
 > methoxyisobutylisonitrile (MIBI) is not retained in the impaired
 > myocardium. The purpose of this study was to determine whether the
 > severity of congestive heart failure (CHF) can be evaluated by use of
 > the washout rate (WR) of MIBI. METHODS AND RESULTS: Seventeen patients
 > with CHF and ten healthy volunteers were enrolled in this study. MIBI
 > and iodine 123 metaiodobenzylguanidine (MIBG) scintigraphy techniques
 > were performed, and the WR was calculated. The blood was also sampled
 > for the measurement of levels of brain natriuretic peptide, which is a

> powerful predictor of the severity of CHF. The WR of MIBI was higher in
> CHF patients (31.2%±6.3%) than in healthy volunteers (25.2%±4.7%)
> (P<.05). There were positive correlations between the WR of MIBI and
> brain natriuretic peptide levels (r=0.723, P<.0001) and a negative
> correlation between the WR of MIBI and the left ventricular ejection
> fraction (r=-0.545, P<.01). The WR of MIBI was correlated with that of
> MIBG (r=0.603, P<.01). CONCLUSIONS: MIBI scintigraphy is useful in
> evaluating the severity of congestive heart failure.

>

> Publication Types:

>

> * Comparative Study

> * Controlled Clinical Trial

>

>

> PMID: 16464718 [PubMed - indexed for MEDLINE]

>

> 4. *** Diagnostic use of second image - English full text not available ***

> Kaku Igaku. 2002 May;39(2):117-24. Related Articles, Links

>

> [Rest delayed images on 99mTc-MIBI myocardial SPECT as a noninvasive
> screen for the diagnosis of vasospastic angina pectoris]

>

> [Article in Japanese]

>

> Ono S, Yamaguchi H, Takayama S, Kurabe A, Heito T.

>

> Department of Radiology, Yamagata Prefectural Shinjo Hospital.

>

> Diagnostic usefulness of 99mTc-MIBI myocardial SPECT at rest was
> examined in 39 cases of coronary vasospastic angina pectoris who were
> diagnosed by a positive reaction to ergonovine provocation. SPECT was
> performed 45 minutes (early image) and 3 hours (delayed image) after the
> intravenous injection of approximately 600 MBq of MIBI. Decrease in
> accumulation was ranked by four defect scores (0: normal; 1: slight
> decrease; 2: moderate decrease; 3: severe decrease) and the total defect
> score was evaluated semiquantitatively. The washout rate between the
> normal area and the spasm area was also evaluated quantitatively using
> bull's eye. As a result, 15 cases (15/39; 38.4%) showed decreased
> accumulation in the early image and 27 cases (27/39; 69.2%) showed
> decreased accumulation in the delayed image. All of the cases which
> showed decreased accumulation in the early image had decreased
> accumulation in the delayed image as well. In 6 cases (6/34; 17.6%)
> showed ST wave changes during exercise ECG and 16 cases (16/34; 47%)
> showed decreased accumulation in the exercise myocardial SPECT. The
> washout rate of MIBI in the decreased accumulation area was
> significantly higher than that of the normal area. Of 32 ergonovine
> induced vasospastic area, 23 areas (72%) exhibited decreased
> accumulation in the delayed image for the same area. Decreased
> accumulation in the delayed image in MIBI was due to the enhanced
> washout, which, in turn, indicated declined retention of MIBI by
> mitochondrial membrane. In coronary vasospastic angina pectoris, spasm
> induced ischemia was thought to have an effect on the mitochondria. This
> study suggested that even with a normal exercise ECG and exercise
> myocardial SPECT, there's a strong possibility of coronary vasospastic
> angina pectoris if a decreased accumulation was found in the delayed

> image in the MIBI myocardial SPECT at rest. Hence, in diagnosing
 > coronary vasospastic angina pectoris, the delayed image in the MIBI
 > myocardial SPECT at rest was believed to be useful.
 >
 > Publication Types:
 >
 > * English Abstract
 >
 >
 > PMID: 12058420 [PubMed - indexed for MEDLINE]
 >
 > 5. *** Diagnostic use of second image - full text not available in my
 > library ***
 > *J Nucl Cardiol. <javascript:AL_get(this, 'jour', 'J Nucl Cardiol. ');>
 > 2001 Nov-Dec;8(6):677-86. Related Articles
 >
 > <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related%20Articles&IdsFromResult=11725264&ordinalpos=26&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
 >
 > Links <javascript:PopUpMenu2_Set(Menu11725264);>
 >
 > Click here to read
 >
 > <<http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?PrId=3048&itool=Abstract-def&uid=11725264&db=pubmed&url=http://linkinghub.elsevier.com/retrieve/pii/S1071-3581%2801%2954260-9>>
 >
 > *Detection of myocardial viability in ischemic-reperfused rat hearts
 > by Tc-99m sestamibi kinetics.*
 >
 > *Liu Z*
 >
 >
 > <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Liu%20Z%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
 > *Johnson G 3rd*
 >
 >
 > <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Johnson%20G%203rd%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
 > *Beju D*
 >
 >
 > <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Beju%20D%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>,
 > *Okada RD*
 >
 >
 > <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Okada%20RD%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract>.
 >
 > William K. Warren Medical Research Institute of the University of
 > Oklahoma Health Sciences Center, Tulsa , USA. zliu@u.arizona.edu
 >
 > BACKGROUND: The purpose of this study was to evaluate technetium 99m
 > sestamibi (MIBI) kinetics in assessing myocardial viability in

> hearts subjected to different ischemia-reperfusion treatments,
 > resulting in graded severity of injury. METHODS AND RESULTS: Sixteen
 > isolated Krebs-Henseleit-perfused rat hearts were divided into 3
 > groups: control (flow, 12 mL/min; n = 5), ischemic-reperfused with
 > glucose (IR+G, n = 6), and ischemic-reperfused without glucose
 > (IR-G, n = 5). MIBI (11.1 mBq [300 microCi]) was infused for 60
 > minutes (uptake), followed by a 60-minute clearance. MIBI uptake
 > (percent injected dose per gram) was significantly decreased in the
 > IR+G (2.07 ± 0.31) and IR-G groups (2.03 ± 0.23 ; P = not
 > significant with IR+G) compared with the control group ($3.06 \pm$
 > 0.25 , P < .05). Fractional washout of MIBI was more rapid in the IR-G
 > group ($72.7\% \pm 3.9\%$, P < .05) than in the control ($21.9\% \pm 1.9\%$)
 > and IR+G groups ($20.3\% \pm 1.7\%$). End retention (percent injected
 > dose per gram) of MIBI in the IR-G (0.60 ± 0.12) and IR+G groups
 > (1.60 ± 0.18) was significantly less than in the control group
 > (2.30 ± 0.11 , P < .05), respectively. The retention in the IR-G
 > group was less than in the IR+G group (P < .05). Creatine kinase
 > assay, triphenyltetrazolium chloride staining, and transmission
 > electron microscopy analysis demonstrated more serious myocardial
 > damage in the IR-G group than in the IR+G group. End MIBI activity
 > was highly correlated with myocardial viability determined by
 > triphenyltetrazolium chloride staining ($r = 0.94$; P < .05) and
 > creatine kinase assay ($r = -0.86$; P < .05). CONCLUSIONS: Clearance of
 > Tc-99m sestamibi is sensitive to metabolic states and may be used
 > for assessment of ongoing myocardial damage.

>
 > PMID: 11725264 [PubMed - indexed for MEDLINE]

> B. SESTAMIBI KINETICS

>
 > 6. *** Rat study of sestamibi kinetics - full text not available in my
 > library ***
 > J Nucl Cardiol. 2001 Nov-Dec;8(6):677-86. Related Articles, Links
 > Click here to read
 > Detection of myocardial viability in ischemic-reperfused rat hearts
 > by Tc-99m sestamibi kinetics.

>
 > Liu Z, Johnson G 3rd, Beju D, Okada RD.

>
 > William K. Warren Medical Research Institute of the University of
 > Oklahoma Health Sciences Center, Tulsa , USA. zliu@u.arizona.edu

>
 > BACKGROUND: The purpose of this study was to evaluate technetium 99m
 > sestamibi (MIBI) kinetics in assessing myocardial viability in hearts
 > subjected to different ischemia-reperfusion treatments, resulting in
 > graded severity of injury. METHODS AND RESULTS: Sixteen isolated
 > Krebs-Henseleit-perfused rat hearts were divided into 3 groups: control
 > (flow, 12 mL/min; n = 5), ischemic-reperfused with glucose (IR+G, n =
 > 6), and ischemic-reperfused without glucose (IR-G, n = 5). MIBI (11.1
 > mBq [300 microCi]) was infused for 60 minutes (uptake), followed by a
 > 60-minute clearance. MIBI uptake (percent injected dose per gram) was
 > significantly decreased in the IR+G (2.07 ± 0.31) and IR-G groups (2.03
 > ± 0.23 ; P = not significant with IR+G) compared with the control group
 > (3.06 ± 0.25 , P < .05). Fractional washout of MIBI was more rapid in the
 > IR-G group ($72.7\% \pm 3.9\%$, P < .05) than in the control ($21.9\% \pm 1.9\%$) and
 > IR+G groups ($20.3\% \pm 1.7\%$). End retention (percent injected dose per

> gram) of MIBI in the IR-G (0.60 ± 0.12) and IR+G groups (1.60 ± 0.18)
 > was significantly less than in the control group (2.30 ± 0.11 , $P < .05$),
 > respectively. The retention in the IR-G group was less than in the IR+G
 > group ($P < .05$). Creatine kinase assay, triphenyltetrazolium chloride
 > staining, and transmission electron microscopy analysis demonstrated
 > more serious myocardial damage in the IR-G group than in the IR+G group.
 > End MIBI activity was highly correlated with myocardial viability
 > determined by triphenyltetrazolium chloride staining ($r = 0.94$; $P < .05$)
 > and creatine kinase assay ($r = -0.86$; $P < .05$). CONCLUSIONS: Clearance of
 > Tc-99m sestamibi is sensitive to metabolic states and may be used for
 > assessment of ongoing myocardial damage.

> PMID: 11725264 [PubMed - indexed for MEDLINE]

> 7. *** Sestamibi kinetics - full text not available in my library***

> Eur J Nucl Med. 2000 Nov;27(11):1632-40. Related Articles, Links

> Click here to read

> A comparison of the overall first-pass kinetics of thallium-201 and

> technetium-99m MIBI in normoxic and low-flow ischaemic myocardium.

> Ayalew A, Marie PY, Menu P, Mertes PM, Hassan N, Danchin N, Olivier
 > P, Karcher G, Bertrand A.

> Department of Nuclear Medicine, UPRES EA 2403, CHU-Nancy, France.

> The specific impact of ischaemia on the myocardial kinetics of
 > thallium-201 and technetium-99m 2-methoxy-2-isobutylisonitrile (MIBI)
 > remains a matter of debate. Using an isolated heart model perfused with
 > red blood cell-enhanced perfusate, we compared the overall first-pass
 > kinetics of 201Tl and MIBI under haemodynamically stable conditions of
 > low-flow ischaemia (> 50% reduction in normal coronary flow and a> or =
 > 20 mmHg fall in systolic contraction pressure, n = 10) and normoxia (n =
 > 11). For both 201Tl and MIBI, we found that under ischaemic conditions
 > (as compared with normoxia) there was a higher initial net extraction
 > fraction (201Tl: 0.78 ± 0.03 vs 0.72 ± 0.06 , $P = 0.006$; MIBI: $0.49 \pm$
 > 0.10 vs 0.39 ± 0.11 , $P = 0.03$), a lower clearance rate in the 30 min
 > following extraction (% decrease in cardiac uptake: 201Tl: 30 ± 12 vs 47
 > ± 14 , $P = 0.02$; MIBI: 5 ± 5 vs 13 ± 11 , $P = 0.02$) and a higher retention
 > fraction at 30 min (201Tl: 0.54 ± 0.10 vs 0.39 ± 0.12 , $P = 0.004$; MIBI:
 > 0.46 ± 0.08 vs 0.33 ± 0.12 , $P = 0.01$). Multivariate analyses, however,
 > revealed that all myocardial kinetic parameters of both tracers were
 > dependent only on coronary flow rates, without any additional
 > significant impact of the presence of ischaemia or states of
 > contractility or oxidative metabolism. We conclude that the myocardial
 > fractional retention of both 201Tl and MIBI is strongly correlated with
 > the decrease in coronary flow during ischaemia. This inverse
 > relationship with coronary flow derives from both the flow-dependent
 > increase in the initial myocardial extraction and the decrease in the
 > subsequent myocardial washout of the tracers.

> Publication Types:



> * Comparative Study

> * Research Support, Non-U.S. Gov't

> PMID: 11105819 [PubMed - indexed for MEDLINE]
 >
 > 8. *** Sestamibi kinetics - full text not available in my library ***
 > Eur J Nucl Med. 1995 Jan;22(1):49-55. Related Articles, Links
 >
 > Washout and redistribution between immediate and two-hour myocardial
 > images using technetium-99m sestamibi.
 >
 > Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R.
 >
 > Universitätsklinikum Rudolf Virchow, Freie Universität Berlin, Germany.
 >
 > The aim of this study was to assess whether a clinically relevant
 > change in myocardial sestamibi activity could be documented within the
 > first 120 min following injection (p.i.). In 17 patients planar anterior
 > imaging of the heart was performed 5 min and 120 min p.i. During this
 > time interval, mean decay-corrected myocardial activity declined to
 > $77.9\% \pm 9.7\%$ after stress and to $85.7\% \pm 7.9\%$ after injection at rest (P
 > < 0.05). In 19 patients with angiographically documented coronary artery
 > disease, single-photon emission tomography was performed 5 min and 120
 > min after injection at maximum stress. For analysis, sestamibi activity
 > was scored semiquantitatively in six left ventricular segments.
 > Furthermore, sestamibi uptake was assessed quantitatively using a
 > circumferential profile method. In 35 of 114 segments the score improved
 > within 120 min p.i. (early fill-in); in these segments relative
 > sestamibi activity rose from $69.9\% \pm 22.5\%$ to $74.5\% \pm 20.8\%$ ($P < 0.01$).
 > In five patients this early fill-in was the only sign of
 > exercise-induced hypoperfusion. In 7 of 114 segments the score
 > deteriorated 120 min p.i. (early tracer washout); in these segments
 > relative sestamibi activity declined from $85.6\% \pm 9.9\%$ to $80.1\% \pm 10.7\%$
 > ($P < 0.02$). In three of four patients with early tracer washout the
 > corresponding coronary artery was significantly narrowed. In conclusion,
 > a global myocardial sestamibi washout was registered within the first
 > 120 min after injection. A fill-in of initial defects as well as an
 > early tracer loss could be detected in a relevant number of patients
 > with chronic coronary artery disease during the first 2 h p.i.(ABSTRACT
 > TRUNCATED AT 250 WORDS)
 >
 > Publication Types:
 >
 > * Comparative Study
 >
 >
 > PMID: 7698155 [PubMed - indexed for MEDLINE]
 >
 >
 > 9. ***Rat study of sestamibi kinetics - full text not yet available from
 > publisher***
 > Ann Nucl Med. 2007 Jul;21(5):267-73. Epub 2007 Jul 25. Related
 > Articles, Links
 > Click here to read
 > Myocardial kinetics of (201)Thallium, (99m)Tc-tetrofosmin, and
 > (99m)Tc-sestamibi in an acute ischemia-reperfusion model using isolated
 > rat heart.
 >
 > Fukushima K, Momose M, Kondo C, Kusakabe K, Kasanuki H.

>
 > Department of Cardiology, Tokyo Women's Medical University, Tokyo,
 > Japan.
 >
 > OBJECTIVE: (201)Thallium (TL), (99m)Tc-tetrofosmin (TF), and
 > (99m)Tc-sestamibi (MIBI) are extensively used as myocardial perfusion
 > agents. The objective of the present study was to evaluate their
 > kinetics under acute ischemia-reperfusion. METHODS: Isolated rat hearts,
 > perfused by the Langendorff method at a constant flow rate of 10 ml/min,
 > were allotted to normal control, mild ischemia, and severe ischemia
 > groups, in which 20-min tracer wash-in was conducted followed by a
 > 25-min tracer washout. No-flow ischemia (15 min for mild ischemia
 > groups; 30 min for severe ischemia groups) was induced before conducting
 > wash-in and washout in the ischemia groups. Whole-heart radioactivity
 > was determined with an external gamma detector. Myocardial flow rate (K
 > (1), ml/min) and clearance rate (k (2), min⁻¹) were calculated.
 > RESULTS: K (1TL), K (1TF), and K (1MIBI) decreased according to the
 > severity of ischemia (K (1TL) 5.32 ± 0.53 , 4.76 ± 0.70 , and 1.44 ± 0.59 ;
 > K (1TF) 3.80 ± 0.70 , 2.73 ± 0.99 , and 1.09 ± 0.45 ; and K (1MIBI) $3.45 \pm$
 > 1.10 , 2.15 ± 0.82 , and 1.05 ± 0.13 , in the normal control, mild, and
 > severe ischemia groups, respectively). K (1) was significantly higher
 > for TL than for the (99m)Tc tracers ($P < 0.05$), but the (99m)Tc tracers
 > had equivalent K (1) values. k (2TL) increased significantly ($P < 0.05$)
 > in the ischemia groups (k (2TL) 0.062 ± 0.013 , 0.11 ± 0.045 , and $0.12 \pm$
 > 0.035), but showed no significant difference between the ischemia
 > groups. k (2MIBI) and k (2TF) were significantly ($P < 0.05$) lower than k
 > (2TL) and increased significantly ($P < 0.05$) in the severe ischemia
 > group (k (2TF) 0.0056 ± 0.0022 , 0.0037 ± 0.0015 , and 0.024 ± 0.015 ; and
 > k (2MIBI) 0.00072 ± 0.0011 , 0.00038 ± 0.00076 , and 0.042 ± 0.034). k
 > (2MIBI) was significantly ($P < 0.05$) lower than k (2TF) in the normal
 > control and mild ischemia groups. CONCLUSIONS: Tracer extraction was
 > higher for TL than for the (99m)Tc tracers and all tracers decreased
 > according to the severity of ischemia-reperfusion in the three tracer
 > groups. The clearance kinetics of not only MIBI but also TF is possibly
 > useful for the evaluation of the severity of ischemia, and the
 > Langendorff method and a methodological approach by continuous
 > determinations of radioactivity may serve for the quantitative analysis
 > of tracer kinetic profiles.
 >
 > PMID: 17634844 [PubMed - in process]
 >
 > --
 > Gordon M. Harrington, Professor Emeritus
 > University of Northern Iowa
 > 3720 Village Place, #6308
 > Waterloo, Iowa 50702-5848
 > Phone: 319-291-8535 Fax: 319-291-8491
 > gordon.harrington@uni.edu dryfly@aya.yale.edu

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> From: gordon.harrington@uni.edu
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> Subject: References 2
>
> 1: Circ Res. 1989 Sep;65(3):632-9. Links
> Comparison of the myocardial uptake of a technetium-labeled
> isonitrile analogue and thallium.
> Leppo JA, Meerdink DJ.
>
> Department of Nuclear Medicine, University of Massachusetts Medical
> Center, Worcester 01655.
>
> The myocardial transmicrovascular transport of thallium-201 (201Tl)
> and technetium-99m hexakis(2-methoxyisobutylisonitrile) (MIBI) were
> compared during variable blood flow levels in nine blood-perfused,
> isolated rabbit hearts. Seventeen injections of radiolabeled albumin and
> EDTA as well as 201Tl and MIBI were performed by indicator-dilution
> techniques. When coronary flow was varied from 0.52 to 3.19 ml/g/min,
> myocardial extraction for MIBI averaged 0.38 +/- 0.09 (SD) whereas 201Tl
> myocardial extraction averaged 0.73 +/- 0.10 (p less than 0.001). Net
> extraction, which was calculated using end points of 1.8-4.9 minutes,
> averaged 0.41 +/- 0.15 for MIBI and was less than the 201Tl net
> extraction of 0.57 +/- 0.13 (p less than 0.001). The mean capillary
> permeability-surface area product for MIBI (0.44 +/- 0.13 ml/g/min) was
> one third of 201Tl (1.30 +/- 0.45 ml/g/min; p less than 0.001). However,
> parenchymal cell permeability-surface area product for MIBI (47.58 +/-
> 25.85 ml/g/min) was much higher than 201Tl (6.52 +/- 6.51 ml/g/min; p
> less than 0.0001), and apparent cellular volume of distribution for MIBI
> (15.15 +/- 3.31 ml/g) was also higher than 201Tl (10.19 +/- 4.00 ml/g; p
> less than 0.01). These data suggest that capillary permeability for
> 201Tl is greater than MIBI, but the reverse is true at the parenchymal
> cell wall. In addition, a new blood-perfused preparation is used for
> indicator-dilution techniques, and previously developed modeling
> analyses are also extended to these experiments.
>
> PMID: 2527638 [PubMed - indexed for MEDLINE]
>
> J Nucl Med. 1989 Sep;30(9):1500-6. Related Articles, Links
> Click here to read
> Comparison of hypoxia and ouabain effects on the myocardial uptake
> kinetics of technetium-99m hexakis 2-methoxyisobutyl isonitrile and
> thallium-201.
>
> Meerdink DJ, Leppo JA.

>
 > Department of Nuclear Medicine, University of Massachusetts Medical
 > Center, Worcester 01655.
 >
 > Effects of hypoxia and ouabain on transcapillary exchange of
 > [^{99m}Tc]hexakis (2-methoxyisobutylisonitrile) [SESTAMIBI, also known as
 > MIBI or HEXAMIBI] and ²⁰¹Tl were investigated with indicator-dilution
 > studies using isolated rabbit hearts. Peak myocardial extraction (Emax),
 > permeability-surface area products (PScap), and net myocardial
 > extraction (Enet) were compared among serial injections during constant
 > coronary flows. Overall, measures of transcapillary transport (Emax and
 > PScap) for SESTAMIBI were significantly lower (p less than 0.001) than
 > those simultaneously determined for thallium, but estimates of tissue
 > retention (Enet) for SESTAMIBI and thallium were not statistically
 > distinguishable. Hypoxia had no significant effect on mean (+/- s.d.)
 > Emax for SESTAMIBI (0.31 +/- 0.13) or thallium (0.59 +/- 0.11), nor on
 > mean PScap or Enet values. Ouabain (1.5 X 10⁻⁷ M and 1.5 X 10⁻⁶ M)
 > had no effect on SESTAMIBI or thallium Emax (respectively, 0.29 +/- 0.08
 > and 0.60 +/- 0.05) or on PScap for SESTAMIBI. Thallium PScap was
 > depressed with higher ouabain dose (control, 1.22 +/- 0.40; high
 > ouabain, 1.06 +/- 0.41 ml/min/g; p less than 0.01). Ouabain also caused
 > a significant and progressive increase in average SESTAMIBI Enet
 > (control, 0.23 +/- 0.10 to high ouabain, 0.33 +/- 0.12; p less than
 > 0.05), but depressed thallium Enet (control, 0.38 +/- 0.14 to high
 > ouabain, 0.32 +/- 0.18; p less than 0.01). These results suggest
 > myocardial metabolic and/or functional status have minor influence on
 > transcapillary transport of SESTAMIBI and thallium, but significantly
 > affects cellular retention.
 >
 > Publication Types:
 >
 > * Comparative Study
 > * In Vitro
 > * Research Support, U.S. Gov't, P.H.S.
 >
 >
 > PMID: 2527973 [PubMed - indexed for MEDLINE]
 >
 > J Am Coll Cardiol. 1989 Dec;14(7):1785-93. Related Articles, Links
 >
 > Effect of ischemia and postischemic dysfunction on myocardial uptake
 > of technetium-99m-labeled methoxyisobutyl isonitrile and thallium-201.
 >
 > Sinusas AJ, Watson DD, Cannon JM Jr, Beller GA.
 >
 > Department of Internal Medicine, University of Virginia Health
 > Sciences Center, Charlottesville 22908.
 >
 > The myocardial uptake of a new technetium-99m-labeled myocardial
 > perfusion agent, methoxyisobutyl isonitrile (Tc-99m MIBI), and
 > thallium-201 was correlated with microsphere flow in an open chest
 > canine model of low coronary flow and postischemic dysfunction. Eighteen
 > dogs were given an injection of thallium-201 (0.5 mCi) and Tc-99m MIBI
 > (5 mCi) either after 40 min of partial left anterior descending artery
 > occlusion (Group I, 10 dogs) or during reperfusion after 15 min of left
 > anterior descending artery occlusion (Group II, 8 dogs). Regional

> dysfunction was documented during injection in both groups by
> quantitative two-dimensional echocardiography. Regional blood flow was
> assessed by radiolabeled microspheres. The heart was excised 15 min
> after radionuclide injection and the left ventricle divided into 96
> segments for gamma well counting. Among Group I dogs, central ischemic
> thallium-201 and Tc-99m MIBI activity (expressed as a percent of the
> activity in the corresponding nonischemic zone) was comparable,
> respectively, for endocardial (54 +/- 17% and 52 +/- 17%), mid-wall (71
> +/- 20% and 69 +/- 17%) and epicardial (89 +/- 13% and 94 +/- 9%)
> segments and increased proportionally with flow. There was a good linear
> correlation among these endocardial segments between flow and both
> thallium-201 ($r = 0.78$) and Tc-99m MIBI ($r = 0.85$) activity. Among Group
> II dogs, central ischemic endocardial flow (59 +/- 14%) was comparable
> to thallium-201 (70 +/- 18%) and Tc-99m MIBI (74 +/- 12%) activity.
> Similarly, relative endocardial flow in the intermediate ischemic region
> (71 +/- 11%) was comparable to thallium-201 (77 +/- 11%) and Tc-99m MIBI
> (81 +/- 10%) activity. Thus, myocardial uptake of Tc-99m MIBI and
> thallium-201 is comparable under conditions of low coronary flow and
> postischemic dysfunction and closely parallels flow alterations.

>

> Publication Types:

>

> * Research Support, Non-U.S. Gov't

> * Research Support, U.S. Gov't, P.H.S.

>

>

> PMID: 2584570 [PubMed - indexed for MEDLINE]

>

> 2: J Nucl Med. 1989 Sep;30(9):1456-63. Related Articles, Links

> Click here to read

> Quantitative planar imaging with technetium-99m methoxyisobutyl

> isonitrile: comparison of uptake patterns with thallium-201.

>

> Sinusas AJ, Beller GA, Smith WH, Vinson EL, Brookeman V, Watson DD.

>

> Department of Internal Medicine, University of Virginia Health

> Sciences Center, Charlottesville 22908.

>

> To compare the myocardial uptake pattern of 99mTc-labeled

> methoxyisobutyl isonitrile [(99mTc] MIBI) and 201TI, planar

> scintigraphy were performed in both patients with documented coronary

> artery disease and subjects with a low likelihood of disease.

> Quantitative analysis was employed using a standard interpolative

> background subtraction algorithm and a new algorithm modified to better

> accommodate for the differences in extracardiac activity seen with

> [99mTc]MIBI rest images. Among patients with coronary artery disease,

> the standard algorithm yielded no significant difference in relative

> defect magnitude between [99mTc]MIBI and 201TI on stress scintigrams (p

> = 0.48), although the magnitude of [99mTc]MIBI defects was greater on

> resting images ($p = 0.02$). When the modified algorithm was employed,

> defect magnitude was similar for both stress ($p = 0.91$) and rest ($p =$

> 0.20) images. Normal segmental uptake ratios derived from a comparison

> of contralateral segments (e.g., septal:posterolateral) in the low

> likelihood patients were similar for both [99mTc]MIBI and 201TI. Thus,

> modification of the standard interpolative background subtraction

> algorithm is necessary for quantitative planar [99mTc]MIBI perfusion

> imaging. When appropriate background subtraction is employed, myocardial
> uptake and quantitative defect magnitude of [99mTc]MIBI and 201TI planar
> images are similar.
>
> Publication Types:
>
> * Comparative Study
> * Research Support, Non-U.S. Gov't
> * Research Support, U.S. Gov't, P.H.S.
>
>
> PMID: 2671298 [PubMed - indexed for MEDLINE]
>
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> Gordon M. Harrington, Professor Emeritus
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FW: tracer comparison rabbits graphics attached

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 > 19: J Nucl Med. 2001 Feb;42(2):272-81. Related Articles, Links
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 >
 > * J Nucl Med. 2001 Feb;42(2):282-4.
 >
 >
 > Kinetic analysis of 125I-iodorotenone as a deposited myocardial flow
 > tracer: comparison with 99mTc-sestamibi.
 >
 > Marshall RC, Powers-Risius P, Reutter BW, Taylor SE, VanBrocklin HF,
 > Huesman RH, Budinger TF.
 >
 > Center for Functional Imaging, E.O. Lawrence Berkeley National
 > Laboratory, University of California, Berkeley 94720, USA.
 >
 > The goal of this investigation was to assess the accuracy of
 > 7'-Z-[125I]iodorotenone (125I-iodorotenone) as a new deposited
 > myocardial flow tracer and compare the results with those for
 > 99mTc-sestamibi. METHODS: The kinetics of these two flow tracers were
 > evaluated in 25 isolated, erythrocyte- and albumin-perfused rabbit
 > hearts over a flow range relevant to patients. The two flow tracers and
 > a vascular reference tracer (131I-albumin) were introduced
 > simultaneously as a compact bolus through a port just above the aortic
 > cannula in the absence of tracer recirculation. Myocardial extraction,
 > retention, washout, and uptake parameters were computed from the venous
 > outflow curves using the multiple-indicator dilution technique and
 > spectral analysis. RESULTS: The extraction of 125I-iodorotenone was much
 > higher than the extraction of 99mTc-sestamibi (0.84 +/- 0.05 vs. 0.48
 > +/- 0.10, respectively, P < 0.001). 125I-iodorotenone extraction was
 > also less affected by flow than was 99mTc-sestamibi (P < 0.001). Net
 > retention of 125I-iodorotenone was significantly greater than
 > 99mTc-sestamibi net retention at 1 min (0.77 +/- 0.08 vs. 0.41 +/- 0.11,
 > respectively, P < 0.001) and 26 min (0.46 +/- 0.13 vs. 0.27 +/- 0.11,
 > respectively, P < 0.001) after tracer injection. Flow had less effect on
 > 125I-iodorotenone net retention than on 99mTc-sestamibi net retention 1
 > min after tracer injection (P < 0.04). However, at 26 min, flow had an
 > equivalent effect on the retention of both flow tracers (P < 0.4). The
 > relationship between 125I-iodorotenone and 99mTc-sestamibi washout was
 > complex and depended on elapsed time after isotope introduction and

> perfusion rate. Reflecting the favorable extraction and retention
> characteristics of 125I-iodorotenone, both its maximum myocardial uptake
> and its 26-min uptake were more closely related to flow than were those
> of 99mTc-sestamibi ($P < 0.001$ for both comparisons). CONCLUSION: The
> extraction and retention of 125I-iodorotenone were greater than those of
> 99mTc-sestamibi, making 125I-iodorotenone the superior flow tracer in
> the isolated rabbit heart.
>
> Publication Types:
>
> * Comparative Study
> * In Vitro
> * Research Support, U.S. Gov't, Non-P.H.S.
> * Research Support, U.S. Gov't, P.H.S.
>
>
> PMID: 11216526 [PubMed - indexed for MEDLINE]
>
> --
> Gordon M. Harrington, Professor Emeritus
> University of Northern Iowa
> 3720 Village Place, #6308
> Waterloo, Iowa 50702-5848
> Phone: 319-291-8535 Fax: 319-291-8491
> gordon.harrington@uni.edu dryfly@aya.yale.edu
>

Re: mibi 5min and 2hr

From:

gordon.harrington@uni.edu

Sent: Mon 2/23/09 3:10 PM

To: RM Fleming (rmfmd7@hotmail.com)

On Thursday 23 August 2007, you wrote:

> And the winner is!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!> Date: Thu, 23 Aug
> 2007 10:39:31 -0500> From: gordon.harrington@uni.edu> To:
> rmfmd7@hotmail.com> Subject: mibi 5min and 2hr> > 29: Eur J Nucl
> Med. 1995 Jan;22(1):49-55. Related Articles, Links> > Washout and
> redistribution between immediate and two-hour myocardial > images
> using technetium-99m sestamibi.> > Richter WS, Cordes M, Calder D,
> Eichstaedt H, Felix R.> > Universitätsklinikum Rudolf Virchow,
> Freie Universität Berlin, Germany.> > The aim of this study was to
> assess whether a clinically relevant > change in myocardial
> sestamibi activity could be documented within the > first 120 min
> following injection (p.i.). In 17 patients planar anterior >
> imaging of the heart was performed 5 min and 120 min p.i. During
> this > time interval, mean decay-corrected myocardial activity
> declined to > 77.9% +/- 9.7% after stress and to 85.7% +/- 7.9%
> after injection at > rest (P < 0.05). In 19 patients with
> angiographically documented > coronary artery disease,
> single-photon emission tomography was performed > 5 min and 120 min
> after injection at maximum stress. For analysis, > sestamibi
> activity was scored semiquantitatively in six left ventricular >
> segments. Furthermore, sestamibi uptake was assessed quantitatively
> > using a circumferential profile method. In 35 of 114 segments the
> score > improved within 120 min p.i. (early fill-in); in these
> segments relative > sestamibi activity rose from 69.9% +/- 22.5% to
> 74.5% +/- 20.8% (P < > 0.01). In five patients this early fill-in
> was the only sign of > exercise-induced hypoperfusion. In 7 of 114
> segments the score > deteriorated 120 min p.i. (early tracer
> washout); in these segments > relative sestamibi activity declined
> from 85.6% +/- 9.9% to 80.1% +/- > 10.7% (P < 0.02). In three of
> four patients with early tracer washout > the corresponding
> coronary artery was significantly narrowed. In > conclusion, a
> global myocardial sestamibi washout was registered within > the
> first 120 min after injection. A fill-in of initial defects as well
> > as an early tracer loss could be detected in a relevant number of
> > patients with chronic coronary artery disease during the first 2
> h > p.i. (ABSTRACT TRUNCATED AT 250 WORDS)> > Publication Types:> >
> * Comparative Study> > > PMID: 7698155 [PubMed - indexed for
> MEDLINE]> > -- > Gordon M. Harrington, Professor Emeritus>
> University of Northern Iowa > 3720 Village Place, #6308> Waterloo,
> Iowa 50702-5848> Phone: 319-291-8535 Fax: 319-291-8491>
> gordon.harrington@uni.edu dryfly@aya.yale.edu > >
>
> Connect to the next generation of MSN Messenger
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Gordon M. Harrington
Professor Emeritus
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Mail: 3720 Village Place, #6308
Waterloo, IA 50702-5848
Phone: 319-291-8535
Fax: 319-291-8491
319-291-8324

Re: FW: mibi 5min and 2hr

From:

gordon.harrington@uni.edu

Sent: Mon 2/23/09 3:11 PM

To: RM Fleming (rmfind7@hotmail.com)

On Thursday 23 August 2007, you wrote:

> Dear Mike,

>

> Search on "sestamibi heart uptake rate" yields no abstract
> references to "uptake rate". References all refer to "uptake" as an
> amount and apply "rate" to "clearance" or "washout". Many
> references see that rate as diagnostic. Whether uptake increases
> after 5-10min seems unaddressed in abstracts. What is concluded is
> that levels can be lower after an hour or more and that differences
> (clearance or washout rate) are diagnostic. I think the answer is
> to list a number of such references with their conclusions quoted.
> I am sending the first of many such abstracts.

>

> In examining the witnesses we can then present the abstracts with
> those conclusions high-lighted. That can probably be done in
> depositions. We may need full text backup for legal purposes. It
> really doesn't matter what the uptake rate is if the tracer does
> not "stick around" for the full 6 hours of the tracers radioactive
> half-life. Clearly articles showing changes in the first few hours,
> show the tracer does not "stick" around. Its relevance will have
> little meaning or understanding for a jury. We simply need to show
> that the medical literature supports changes in the two images over
> time, whether it is due to uptake or washout or something
> completely unknown to mankind. No one will doubt that gravity
> exists, yet none of the jurors can define it. The first person who
> does will get the Nobel Prize, yet no one doubts its existence.
> The medical literature supports having information provided by two
> images, since the papers to follow show changes over serial images.

>

> > 29: Eur J Nucl Med. 1995 Jan;22(1):49-55. Related Articles,
> > Links> > Washout and redistribution between immediate and
> > two-hour myocardial > images using technetium-99m sestamibi.> >
> > Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R.> >
> > Universitätsklinikum Rudolf Virchow, Freie Universität Berlin,
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> > patients this early fill-in was the only sign of >
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> > with early tracer washout > the corresponding coronary artery
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> > sestamibi washout was registered within > the first 120 min
> > after injection. A fill-in of initial defects as well > as an
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> > patients with chronic coronary artery disease during the first 2
> > h > p.i.(ABSTRACT TRUNCATED AT 250 WORDS)> > Publication Types:>
> > * Comparative Study> > > PMID: 7698155 [PubMed - indexed for
> > MEDLINE]
>
> I will be forwarding a number of abstracts to you without
> additional intro or closure.> Yours,
>
> Dr. Fleming
>
> _____
> Invite your mail contacts to join your friends list with Windows
> Live Spaces. It's easy!
> http://spaces.live.com/spacesapi.aspx?wx_action=create&wx_url=/friends.aspx&mkt=en-us

--

Gordon M. Harrington
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Mail: 3720 Village Place, #6308
Waterloo, IA 50702-5848
Phone: 319-291-8535
Fax: 319-291-8491
319-291-8324

FW: inflammation and the thymus gland showing anterior imaging

From: **RM Fleming** (rmfmd7@hotmail.com)

Sent: Mon 2/23/09 3:12 PM

To: Mike Hansen PD corrected (mike_hansen@fd.org); Richard Fleming (rmfmd7@hotmail.com)

Updating your files from this one for articles:

> On Thursday 28 June 2007, you wrote:

>> Dear Mike,

>>

>> Published paper on the thymus gland and inflammation. You should
>> already have numerous peer review manuscripts published in the
>> medical literature but I thought you might like one more showing
>> SPECT camera utilization of a static anterior image showing the
>> thymus for those nuclear medicine doctors who have been questioned
>> by the feds and said they were unaware of any published papers.

>>

>> <http://radiology.rsna.org/cgi/reprint/227/2/353>

>>

>> I also think that the cardiologist (Dr. Stephen Michael O'Connor)
>> was involved in a malpractice suit against me where the patient's
>> angina went away when she took my medication and returned when she
>> stopped taking it. He (O'Connor-if this is the same cardiologist)
>> told the patient I couldn't tell her she had heart disease without
>> a cardiac cath. Clearly, he not only is not up on current
>> technology, but the Judge dismissed the case with prejudice.

>>

>> Yours,

>>

>> Dr. Fleming

not superglue

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 2/23/09 10:42 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

Here you go. There are other articles which I sent you from June 2007 -> Feb 2008 which are also important. I will look for these.

- 1) Blumgart and Yens 1926, publish paper on "Circulation Time."
- 2) Maublant JC, Gachon P, Moins N. Hexakis (2-methoxy isobutylisonitrile) technetium-99m and thallium-201 chloride: uptake and release in cultured myocardial cells. J Nucl Med 1988; 29(1):48-54. Proves washout of sestamibi in non-ischemic tissue is 28 minutes (enough for 2 washouts in 55 minutes).
- 3) Li Q-S, Solot G, Frank TL, Wagner HN, and Becker LC. Myocardial redistribution of technetium-99m-methoxyisobutyl isonitrile (sestamibi), J Nucl Med 1990;31:1069-1075. Proves that sestamibi washes out (redistributes) even faster than the 28 minutes noted by Maublant, when ischemia is present.
- 4) Crane P, Laliberte R, Heminway S, Thoolen M, Orlandi C. Effect of mitochondrial viability and metabolism on technetium-99m-sestamibi myocardial retention. Eur J Nucl Med 1993;20:20-25. A study paid for by Dupont who owned sestamibi proves that the reason sestamibi washes out sooner in ischemic tissue than non-ischemic tissue, is that ischemic tissue has mitochondrial calcium overload which results in faster washout of sestamibi.

All these studies show sestamibi doesn't go in and stick like superglue; but, rather washes out in normal tissue in 28 minutes and even faster in regions with coronary artery disease. The Blumgart paper was the original nuclear cardiology paper showing serial collection of data was the way to go!

These are the 28 other papers referenced. They show the importance of looking at washout under different conditions. If sestamibi washes out with cancer, it will washout of other tissue. It is the mitochondria present

in cancers, ischemic tissue and normal tissue which the sestamibi washes in and out of!!!

1. Pace L, Catalano L, Del Vecchio S, et al. Washout of [99mTc] sestamibi in predicting response to chemotherapy in patients with multiple myeloma. *Q J Nucl Med Mol Imaging* 2005;49:281-5.
2. Hurwitz GA, Ghali SK, Husni M, et al. Pulmonary uptake of Technetium-99m-Sestamibi induced by dipyridamole-based stress or exercise. *J Nucl Med* 1998;39:339-45.
3. Hurwitz GA, Fox SP, Driedger AA, Willems C, Powe JE. Pulmonary uptake of sestamibi on early post-stress images: angiographic relationships, incidence and kinetics. *Nucl Med Commun* 1993;14:15-22.
4. Saha M, Forrest TF, Brown KA. Lung uptake of technetium-99m-sestamibi: relation to clinical, exercise, hemodynamic, and left ventricular function variables. *J Nucl Cardiol* 1994;1:52-6.
5. Giubbini R, Bampini R, Milan E, et al. Evaluation of technetium-99m-sestamibi lung uptake: correlation with left ventricular function. *J Nucl Med* 1995;36:58-63.
6. Sugiura T, Takase H, Toriyama T, et al. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.
7. Kumita S, Seino Y, Cho K, et al. Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison with normal control. *Ann Nucl Med* 2002;16:237-42.
8. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. *J Nucl Cardiol* 2007;14:215-20.
9. Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.
10. Ikawa M, Kawai Y, Arakawa K, et al. Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of 99mTc-MIBI washout and 123I-BMIPP/99mTc-MIBI mismatch. *Mitochondrion* 2007;7:164-70.
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12. Ono S, Yamaguchi H, Takayama S, Kurabe A, Heito T. Rest delayed images on 99mTc-MIBI myocardial SPECT as a noninvasive screen for the diagnosis of vasospastic angina pectoris. *Kaku Igaku* 2002;39:117-24.
13. Ono S, Yakeishi Y, Yamaguchi H, et al. Enhanced regional washout of technetium-99m-sestamibi in patients with coronary spastic angina. *Ann Nucl Med* 2003;17:393-8.
14. Fukushima K, Momose M, Kondo C, et al. Myocardial kinetics of (201) Thallium, (99m) Tc-tetrofosmin, and (99m) Tc-sestamibi in an acute ischemia-reperfusion model using isolated rat heart. *Ann Nucl Med* 2007;21:267-73.
15. VanBrocklin HF, Hanrahan SM, Enas JD, et al. Mitochondrial avid radioprobes. Preparation and evaluation of 7(Z)-[125I]iodorotenone and 7(Z)-[125I]iodorotenol. *Nucl Med Biol* 2007;34:109-16.
16. Tanaka R, Nakamura T, Chiba S, et al. Clinical implication of reverse redistribution on 99mTc-sestamibi images for evaluating ischemic heart disease. *Ann Nucl Med* 2006;20:349-56.
17. Liu Z, Johnson G 3rd, Beju D, Okada RD. Detection of myocardial viability in ischemic-reperfused rat hearts by Tc-99m sestamibi kinetics. *J Nucl Cardiol* 2001;8:677-86.
18. Shin WJ, Miller K, Stipp V, Mazour S. Reverse redistribution on dynamic exercise and dipyridamole stress technetium-99m-MIBI myocardial SPECT. *J Nucl Med* 1995;36:2053-5.
19. Takeishi Y, Sukekawa H, Fujiwara S, et al. Reverse redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial infarction. *J Nucl Med* 1996;37:1289-94.
20. Fujiwara S, Takeishi Y, Atsumi H, et al. Prediction of functional recovery in acute myocardial infarction: comparison between sestamibi reverse redistribution and sestamibi/BMIPP mismatch. *J Nucl Cardiol* 1998;5:119-27.
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23. Meerdink DJ, Leppo JA. Myocardial transport of hexakis(2-methoxyisobutyl isonitrile) and thallium before and after coronary reperfusion. *Circulation Research* 1990;66:1738-46.
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25. Takahashi N, Reinhardt CP, Marcel R, Leppo JA. Myocardial uptake of 99m Tc-tetrofosmin, Sestamibi, and 201 Tl in a model of acute coronary reperfusion. *Circulation* 1996;94:2605-13.

Dr. Fleming

FW: mibi 5min and 2hr

From: **RM Fleming** (rmfmd7@hotmail.com)
 Sent: Mon 2/23/09 11:21 PM
 To: Mike Hansen PD corrected (mike_hansen@fd.org)

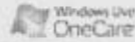
> From: gordon.harrington@uni.edu
 > To: rmfmd7@hotmail.com
 > Subject: Re: FW: mibi 5min and 2hr
 > Date: Mon, 23 Feb 2009 17:11:11 -0600
 >
 > On Thursday 23 August 2007, you wrote:
 >> Dear Mike,
 >>
 >> Search on "sestamibi heart uptake rate" yields no abstract
 >> references to "uptake rate". References all refer to "uptake" as an
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 >>> 29: Eur J Nucl Med. 1995 Jan;22(1):49-55. Related Articles,
 >>> Links>> Washout and redistribution between immediate and
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 >>> Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R.>>
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 >>> the heart was performed 5 min and 120 min p.i. During this>
 >>> time interval, mean decay-corrected myocardial activity declined
 >>> to> 77.9% +/- 9.7% after stress and to 85.7% +/- 7.9% after
 >>> injection at> rest (P < 0.05). In 19 patients with
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>>> single-photon emission tomography was performed> 5 min and 120
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>>>> * Comparative Study>>> PMID: 7698155 [PubMed - indexed for
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>>
>> I will be forwarding a number of abstracts to you without
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>>
>> Dr. Fleming

papers

From: **RM Fleming** (rmfmd7@hotmail.com)
 Sent: Tue 2/24/09 2:41 AM
 To: Mike Hansen PD corrected (mike_hansen@fd.org)

 5 attachments



[Vol 5 #2 ...doc](#) (53.6 KB), [Evaluatio...html](#) (2.2 KB), [JCI - STU...html](#) (7.2 KB), [jcinvest0...pdf](#) (1461.5 KB), [Paper 1.jpg](#) (2.4 MB)

Mike,

There will be a series of emails sent to you with multiple papers. This is the first page only to reduce scanning. I know there are other papers we have talked about including a paper by Dr. Kim Williams on incidental findings made on the static images which included thymomas (thymus). I cannot find my copy. I did find a case report of this. There is also the paper from this summer where the Iranian group showed that multiple post-stress images yielded so much better information that they called for changing how we do studies.

If you need more, let me know. From the 28 papers usually cited, plus the abstracts sent to you earlier and these papers, you should have ~ 50 papers looking at multiple post-stress sestamibi imaging in addition to thymus and other organ (incidental detection). I will begin the attachments with vol 5, #2, which is my paper to be published (peer-reviewed journal) on May 1, 2009 in the DeBakey Methodist journal.

Yours,

Dr. Fleming

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STUDIES ON THE VELOCITY OF BLOOD FLOW

J. Clin. Invest. Herrmann L. Blumgart, et al. 4:1 doi:10.1172/JCI100106 [Go to this article.]

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articles part 2

From: **RM Fleming** (rmfmd7@hotmail.com)

Sent: Tue 2/24/09 2:45 AM

To: Mike Hansen PD corrected (mike_hansen@fd.org)

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mibi clearance rate

From: gordon.harrington@uni.edu

Sent: Wed 8/22/07 10:22 PM

To: rmfmd7@hotmail.com

1: Ann Nucl Med. 2007 Jul;21(5):267-73. Epub 2007 Jul 25. Related Articles, Links

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Myocardial kinetics of (201)Thallium, (99m)Tc-tetrofosmin, and (99m)Tc-sestamibi in an acute ischemia-reperfusion model using isolated rat heart.

Fukushima K, Momose M, Kondo C, Kusakabe K, Kasanuki H.

Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan.

OBJECTIVE: (201)Thallium (TL), (99m)Tc-tetrofosmin (TF), and (99m)Tc-sestamibi (MIBI) are extensively used as myocardial perfusion agents. The objective of the present study was to evaluate their kinetics under acute ischemia-reperfusion. **METHODS:** Isolated rat hearts, perfused by the Langendorff method at a constant flow rate of 10 ml/min, were allotted to normal control, mild ischemia, and severe ischemia groups, in which 20-min tracer wash-in was conducted followed by a 25-min tracer washout. No-flow ischemia (15 min for mild ischemia groups; 30 min for severe ischemia groups) was induced before conducting wash-in and washout in the ischemia groups. Whole-heart radioactivity was determined with an external gamma detector. Myocardial flow rate (K (1), ml/min) and clearance rate (k (2), min⁻¹) were calculated. **RESULTS:** K (1TL), K (1TF), and K (1MIBI) decreased according to the severity of ischemia (K (1TL) 5.32 +/- 0.53, 4.76 +/- 0.70, and 1.44 +/- 0.59; K (1TF) 3.80 +/- 0.70, 2.73 +/- 0.99, and 1.09 +/- 0.45; and K (1MIBI) 3.45 +/- 1.10, 2.15 +/- 0.82, and 1.05 +/- 0.13, in the normal control, mild, and severe ischemia groups, respectively). K (1) was significantly higher for TL than for the (99m)Tc tracers (P < 0.05), but the (99m)Tc tracers had equivalent K (1) values. k (2TL) increased significantly (P < 0.05) in the ischemia groups (k (2TL) 0.062 +/- 0.013, 0.11 +/- 0.045, and 0.12 +/- 0.035), but showed no significant difference between the ischemia groups. k (2MIBI) and k (2TF) were significantly (P < 0.05) lower than k (2TL) and increased significantly (P < 0.05) in the severe ischemia group (k (2TF) 0.0056 +/- 0.0022, 0.0037 +/- 0.0015, and 0.024 +/- 0.015; and k (2MIBI) 0.00072 +/- 0.0011, 0.00038 +/- 0.00076, and 0.042 +/- 0.034). k (2MIBI) was significantly (P < 0.05) lower than k (2TF) in the normal control and mild ischemia groups. **CONCLUSIONS:** Tracer extraction was higher for TL than for the (99m)Tc tracers and all tracers decreased according to the severity of ischemia-reperfusion in the three tracer groups. The clearance kinetics of not only MIBI but also TF is possibly useful for the evaluation of the severity of ischemia, and the Langendorff method and a methodological approach by continuous determinations of radioactivity may serve for the quantitative analysis of tracer kinetic

Q ↓ severity of ischemia

↓ tracer extraction
Severity of ischemia
Clearance kinetics (i.e.
washout) may be useful to
determine severity of ischemia

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mibi WOR

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4: Mitochondrion. 2007 Feb-Apr;7(1-2):164-70. Epub 2006 Dec 5.
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Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of 99mTc-MIBI washout and 123I-BMIPP/99mTc-MIBI mismatch.

Ikawa M, Kawai Y, Arakawa K, Tsuchida T, Miyamori I, Kuriyama M, Tanaka M, Yoneda M.

Second Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, 23-3 Shimoaiduki, Matsuoka, Fukui 910-1193, Japan.

Cardiomyopathy is one of the main features that determines prognosis in patients with mitochondrial encephalomyopathy. We investigated respiratory chain failure using 99mTc-MIBI- and 123I-BMIPP-SPECT in vivo in five patients with mitochondrial cardiomyopathy. With the lowering of cardiac function, the 99mTc-MIBI-washout rate (WOR) increased, and the 99mTc-MIBI-uptake decreased, conversely. In patients who showed severe cardiac involvement, 99mTc-MIBI-uptake was markedly reduced, and by contrast, 123I-BMIPP-uptake increased (123I-BMIPP/99mTc-MIBI mismatch). There were significant correlations between the WOR on 99mTc-MIBI-SPECT and interventricular septal thickness (IVST) on echocardiography and between WOR and left ventricular ejection fraction (LVEF) on 99mTc-MIBI-SPECT. The increased WOR and decreased uptake of 99mTc-MIBI were reflected by the lowered mitochondrial membrane potential created by mitochondrial respiratory chain whereas 123I-BMIPP/99mTc-MIBI mismatch may be created by the enhanced triglyceride-pool. These nuclear medicine techniques are the potential tools to evaluate the energy state in mitochondrial cardiomyopathy.

*6 Cardiac-fxn = ↓ mibi uptake
 ↑ washout
 (- lower counts + faster
 loss of counts)*

PMID: 17280875 [PubMed - indexed for MEDLINE]

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mibi comparison reference

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5: Nucl Med Biol. 2007 Jan;34(1):109-16. Epub 2006 Nov 28. Related Articles, Links

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Mitochondrial avid radioprobes. Preparation and evaluation of 7'(Z)-[125I]iodorotenone and 7'(Z)-[125I]iodorotenol.

VanBrocklin HF, Hanrahan SM, Enas JD, Nandanan E, O'Neill JP.

Department of Functional Imaging, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA. hfvanbrocklin@lbl.gov

The loss of mitochondrial function has been implicated in a number of maladies such as Huntington's disease, Parkinson's disease (PD), cancer and cardiovascular disease. The objective of this research was to develop a radiolabeled mitochondrial probe. Two tracers, 7'-Z-iodorotenol and 7'-Z-iodorotenone, analogs of rotenone a natural product that inhibits Complex I of the mitochondrial electron transport chain, have been labeled with iodine-125 in 45-85% yield in a single step from the corresponding tributylstannyl precursor. In vivo distribution in adult male Sprague-Dawley rats for both compounds showed high accumulation in the heart (1.7-3.7 %ID/g at 1 h), a tissue with high mitochondrial content. Z-iodorotenol did not washout of most tissues between 1 and 2 h postinjection, whereas Z-iodorotenone showed moderate washout (7-26%) over the same period. By 24 h, there was significant loss of both compounds from most tissues including the heart. Heart-to-blood, -lung and -liver ratios for Z-iodorotenone of 28.9, 10.7 and 2.4, respectively, were two- to fourfold higher than the Z-iodorotenol ratios. Compared to the current clinical perfusion tracers, 99mTc-sestamibi and 99mTc-tetrofosmin, Z-iodorotenone demonstrates similar 1 h heart accumulation and significantly higher heart-to-lung ratio ($P < .001$). Z-iodorotenone heart-to-liver ratio is equivalent to 99mTc-sestamibi. 7'-Z-iodorotenone possesses distribution characteristics of an improved tracer for SPECT perfusion studies.

Heart 02.

inhibits mitochondria

1-2" constant

H.L. Ratios

equivalent to mibi

Publication Types:

- * Evaluation Studies
- * Research Support, N.I.H., Extramural
- * Research Support, U.S. Gov't, Non-P.H.S.

PMID: 17210467 [PubMed - indexed for MEDLINE]

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mibi delayed

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7: Ann Nucl Med. 2006 Jun;20(5):349-56. Related Articles, Links

Clinical implication of reverse redistribution on 99mTc-sestamibi images for evaluating ischemic heart disease.

Tanaka R, Nakamura T, Chiba S, Ono T, Yoshitani T, Miyamoto A, Yamazaki J.

Radiological Department, Kushiro-shi Ishikai Hospital, Hokkaido, Japan. r_tanaka@kushiro-ishikai.or.jp

OBJECTIVE: The purpose of this study was to clarify the usefulness of 99mTc-sestamibi (MIBI) delayed imaging in the assessment of the severity of myocardial ischemia in patients with coronary artery stenosis. **METHODS:** Forty-three angina pectoris with coronary stenosis of greater than 75% were enrolled in this study. Myocardial perfusion SPECT images were obtained 1 and 6 hours after an intravenous injection of MIBI at rest. Stress myocardial perfusion SPECT images were also acquired after the injection of MIBI. And myocardial fatty acid metabolism images were obtained 30 minutes after the injection of BMIPP at rest. Myocardial perfusion SPECT images were divided into 20 segments which were semiquantitatively assessed according to a 4-level defect score scale: score 0 (normal) to score 3 (severely); then the extent score (ES) and severity score (SS) were calculated. **RESULTS:** The sensitivity for myocardial ischemia showed the highest rate at 88.3% with MIBI delayed SPECT. According to the coronary angiography findings, MIBI stress SPECT and MIBI delayed SPECT detected the severity and extent of ischemia with more sensitivity than MIBI early SPECT in 12 patients (group A) with stenosis of more than 75% but less than 90% ($p < 0.01$). Even though MIBI stress SPECT detected the severity and extent of ischemia in 31 patients (group B) with stenosis of more than 90% but less than 100%, there was no significant difference between MIBI stress SPECT and MIBI delayed SPECT. BMIPP SPECT revealed significant differences between group A and group B regarding the severity of myocardial ischemia. MIBI reverse redistribution was observed in 33 patients and no significant difference existed between groups A and B. **CONCLUSIONS:** Myocardial washout of MIBI was frequently observed in patients with angina pectoris and the detection accuracy for ischemia was high. MIBI imaging is considered useful for assessment not only of myocardial perfusion but also mitochondrial function. The imagings with BMIPP and delayed MIBI could serve to determine the severity of myocardial ischemia more accurately.

Not detection of ischemia

Washout observed = ischemia

Publication Types:

* Clinical Trial

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mibi washout useful

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8: J Nucl Cardiol. 2006 Jan-Feb;13(1):64-8. Related Articles, Links
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Usefulness of Tc-99m methoxyisobutylisnitrile scintigraphy for
evaluating congestive heart failure.

Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y.

Department of Internal Medicine, Enshu General Hospital, Hamamatsu,
and Department of Internal Medicine and Molecular Science, Graduate
School of Medical Sciences, Nagoya City University, Japan.

BACKGROUND: Evidence is accumulating that technetium 99m
methoxyisobutylisnitrile (MIBI) is not retained in the impaired
myocardium. The purpose of this study was to determine whether the
severity of congestive heart failure (CHF) can be evaluated by use of
the washout rate (WR) of MIBI. **METHODS AND RESULTS:** Seventeen patients
with CHF and ten healthy volunteers were enrolled in this study. MIBI
and iodine 123 metaiodobenzylguanidine (MIBG) scintigraphy techniques
were performed, and the WR was calculated. The blood was also sampled
for the measurement of levels of brain natriuretic peptide, which is a
powerful predictor of the severity of CHF. The WR of MIBI was higher in
CHF patients (31.2% +/- 6.3%) than in healthy volunteers (25.2% +/- 4.7%)
($P < .05$). There were positive correlations between the WR of MIBI and
brain natriuretic peptide levels ($r = 0.723$, $P < .0001$) and a negative
correlation between the WR of MIBI and the left ventricular ejection
fraction ($r = -0.545$, $P < .01$). The WR of MIBI was correlated with that of
MIBG ($r = 0.603$, $P < .01$). **CONCLUSIONS:** MIBI scintigraphy is useful in
evaluating the severity of congestive heart failure.

impaired mitochondria

MIBI washout = CHF

Publication Types:

- * Comparative Study
- * Controlled Clinical Trial

PMID: 16464718 [PubMed - indexed for MEDLINE]

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Fleming Motion to Vacate - Appendix

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mibi 10min and 60min

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10: J J Nucl Med Mol Imaging. 2005 Sep;49(3):281-5. Related Articles, Links

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Washout of [99mTc] sestamibi in predicting response to chemotherapy in patients with multiple myeloma.

Pace L, Catalano L, Del Vecchio S, De Renzo A, Fonti R, Salvatore B, Andretta C, Di Nuzzo C, Rotoli B, Salvatore M.

Nuclear Medicine Unit, Department of Biomorphological and Functional Sciences, Federico II University, Naples, Italy. pace@unina.it

AIM: Technetium-99m 2-methoxy-isobutyl-isonitrile ([99mTc] MIBI) has been successfully used to study patients with multiple myeloma (MM). This tracer is also a substrate for P-glycoprotein (Pgp). Since Pgp overexpression is one of the primary mechanisms of multidrug resistance in MM, the aim of this study was to test whether [99mTc] MIBI could be an index of Pgp overexpression and function in MM and therefore predicts response to chemotherapy. METHODS: Forty patients with MM (12 in stage I, 15 in stage II, and 13 in stage III) showing diffuse bone marrow [99mTc] MIBI uptake were included in the study. All patients underwent whole body scintigraphy at 10 and 60 minutes after i.v. injection of 555 MBq of [99mTc] MIBI. [99mTc] MIBI washout was measured, after decay correction, as: (10 minute counts/pixel minus 60 minute counts/pixel) divided by 10 minute counts/pixel, computed on a region of interest drawn on the thoracic spine (posterior projection), taking care of avoiding heart and splanchnic organs. Disease restaging was performed at a mean time of 32+/-20 months, and patients were considered to be in remission (complete or partial) or to show disease progression on the basis of a complete clinical and hematological evaluation. RESULTS: Patients showing disease progression at restaging (n=26) had higher washout (19.3+/-9.8% vs 12.8+/-6.9%, p<0.05) than patients in remission (n=14). Disease free survival was significantly better in patients with lower washout of [99mTc] MIBI. No differences in therapeutic regimen and stage of disease at admission were found between the 2 groups. When patients treated with melphalan were excluded from the analysis, 87.5% of patients in remission had low washout. CONCLUSIONS: The present study suggests a potential role of [99mTc] MIBI washout in predicting response to chemotherapy in patients with MM.

5'60'
washout allows
determination of
response to
chemo

Publication Types:

* Clinical Trial

PMID: 16172574 [PubMed - indexed for MEDLINE]

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mibi clearance rats

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18: J Nucl Cardiol. 2001 Nov-Dec;8(6):677-86. Related Articles, Links
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Detection of myocardial viability in ischemic-reperfused rat hearts
by Tc-99m sestamibi kinetics.

Liu Z, Johnson G 3rd, Beju D, Okada RD.

William K. Warren Medical Research Institute of the University of
Oklahoma Health Sciences Center, Tulsa, USA. zliu@u.arizona.edu

BACKGROUND: The purpose of this study was to evaluate technetium 99m sestamibi (MIBI) kinetics in assessing myocardial viability in hearts subjected to different ischemia-reperfusion treatments, resulting in graded severity of injury. **METHODS AND RESULTS:** Sixteen isolated Krebs-Henseleit-perfused rat hearts were divided into 3 groups: control (flow, 12 mL/min; n = 5), ischemic-reperfused with glucose (IR+G, n = 6), and ischemic-reperfused without glucose (IR-G, n = 5). MIBI (11.1 mBq [300 microCi]) was infused for 60 minutes (uptake), followed by a 60-minute clearance. MIBI uptake (percent injected dose per gram) was significantly decreased in the IR+G (2.07 +/- 0.31) and IR-G groups (2.03 +/- 0.23; P = not significant with IR+G) compared with the control group (3.06 +/- 0.25, P < .05). Fractional washout of MIBI was more rapid in the IR-G group (72.7% +/- 3.9%, P < .05) than in the control (21.9% +/- 1.9%) and IR+G groups (20.3% +/- 1.7%). End retention (percent injected dose per gram) of MIBI in the IR-G (0.60 +/- 0.12) and IR+G groups (1.60 +/- 0.18) was significantly less than in the control group (2.30 +/- 0.11, P < .05), respectively. The retention in the IR-G group was less than in the IR+G group (P < .05). Creatine kinase assay, triphenyltetrazolium chloride staining, and transmission electron microscopy analysis demonstrated more serious myocardial damage in the IR-G group than in the IR+G group. End MIBI activity was highly correlated with myocardial viability determined by triphenyltetrazolium chloride staining (r = 0.94; P < .05) and creatine kinase assay (r = -0.86; P < .05). **CONCLUSIONS:** Clearance of Tc-99m sestamibi is sensitive to metabolic states and may be used for assessment of ongoing myocardial damage.

PMID: 11725264 [PubMed - indexed for MEDLINE]

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① ↓ mibi uptake in ischemia
② ↓ washout > ischemia
③ ↓ mibi retention in ischemia
ischemic damage

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mibi washout rate

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13: Ann Nucl Med. 2002 Jun;16(4):237-42. Related Articles, Links

Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison with normal control.

Kumita S, Seino Y, Cho K, Nakajo H, Toba M, Fukushima Y, Okamoto N, Takano T, Kumazaki T.

Department of Radiology, Nippon Medical School, Tokyo, Japan.
s-kumita@nms.ac.jp

BACKGROUND: In contrast to 201TlCl, 99mTc-sestamibi shows very slow myocardial clearance after its initial myocardial uptake. In the present study, myocardial washout of 99mTc-sestamibi was calculated in patients with non-ischemic chronic heart failure (CHF) and compared with biventricular parameters obtained from first-pass and ECG-gated myocardial perfusion SPECT data. **METHODS AND RESULTS:** After administration of 99mTc-sestamibi, 25 patients with CHF and 8 normal controls (NC) were examined by ECG-gated myocardial perfusion SPECT and planar data acquisition in the early and delayed (interval of 3 hours) phase. Left ventricular ejection fraction (LVEF, %), peak filling rate (PFR, sec⁻¹), end-diastolic volume (LVEDV, ml) and end-systolic volume (LVESV, ml) were automatically calculated from the ECG-gated SPECT data. Myocardial washout rates over 3 hours were calculated from the early and delayed planar images. Myocardial washout rates in the CHF group (39.6±5.2%) were significantly higher than those in the NC group (31.2±5.5%, $p < 0.01$). The myocardial washout rates for the 33 subjects showed significant correlations with LVEF ($r = -0.61$, $p < 0.001$), PFR ($r = -0.47$, $p < 0.01$), LVEDV ($r = 0.45$, $p < 0.01$) and LVESV ($r = 0.48$, $p < 0.01$). **CONCLUSION:** The myocardial washout rate of 99Tc-sestamibi is considered to be a novel marker for the diagnosis of myocardial damage in patients with chronic heart failure.

Ref 19-21
mibi - CAD
addition

Washout = damage / 100

Publication Types:

- * Clinical Trial
- * Comparative Study
- * Controlled Clinical Trial
- * Research Support, Non-U.S. Gov't

PMID: 12126092 [PubMed - indexed for MEDLINE]


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part 4

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Delayed image mibi text unavailable

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15: Kaku Igaku. 2002 May;39(2):117-24. Related Articles, Links

[Rest delayed images on 99mTc-MIBI myocardial SPECT as a noninvasive screen for the diagnosis of vasospastic angina pectoris]

[Article in Japanese]

Ono S, Yamaguchi H, Takayama S, Kurabe A, Helto T.

Department of Radiology, Yamagata Prefectural Shinjo Hospital.

Diagnostic usefulness of 99mTc-MIBI myocardial SPECT at rest was examined in 39 cases of coronary vasospastic angina pectoris who were diagnosed by a positive reaction to ergonovine provocation. SPECT was performed 45 minutes (early image) and 3 hours (delayed image) after the intravenous injection of approximately 600 MBq of MIBI. Decrease in accumulation was ranked by four defect scores (0: normal; 1: slight decrease; 2: moderate decrease; 3: severe decrease) and the total defect score was evaluated semiquantitatively. The washout rate between the normal area and the spasm area was also evaluated quantitatively using bull's eye. As a result, 15 cases (15/39; 38.4%) showed decreased accumulation in the early image and 27 cases (27/39; 69.2%) showed decreased accumulation in the delayed image. All of the cases which showed decreased accumulation in the early image had decreased accumulation in the delayed image as well. In 6 cases (6/34; 17.6%) showed ST wave changes during exercise ECG and 16 cases (16/34; 47%) showed decreased accumulation in the exercise myocardial SPECT. The washout rate of MIBI in the decreased accumulation area was significantly higher than that of the normal area. Of 32 ergonovine induced vasospastic area, 23 areas (72%) exhibited decreased accumulation in the delayed image for the same area. Decreased accumulation in the delayed image in MIBI was due to the enhanced washout, which, in turn, indicated declined retention of MIBI by mitochondrial membrane. In coronary vasospastic angina pectoris, spasm induced ischemia was thought to have an effect on the mitochondria. This study suggested that even with a normal exercise ECG and exercise myocardial SPECT, there's a strong possibility of coronary vasospastic angina pectoris if a decreased accumulation was found in the delayed image in the MIBI myocardial SPECT at rest. Hence, in diagnosing coronary vasospastic angina pectoris, the delayed image in the MIBI myocardial SPECT at rest was believed to be useful.

*Delayed image useful to
detect vasospasm*

Publication Types:

* English Abstract

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clearance rate thallium mibi

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20: Eur J Nucl Med. 2000 Nov;27(11):1632-40. Related Articles, Links
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A comparison of the overall first-pass kinetics of thallium-201 and technetium-99m MIBI in normoxic and low-flow ischaemic myocardium.

Ayalew A, Marie PY, Menu P, Mertes PM, Hassan N, Danchin N, Olivier P, Karcher G, Bertrand A.

Department of Nuclear Medicine, UPRES EA 2403, CHU-Nancy, France.

The specific impact of ischaemia on the myocardial kinetics of thallium-201 and technetium-99m 2-methoxy-2-isobutylisonitrile (MIBI) remains a matter of debate. Using an isolated heart model perfused with red blood cell-enhanced perfusate, we compared the overall first-pass kinetics of 201Tl and MIBI under haemodynamically stable conditions of low-flow ischaemia (> 50% reduction in normal coronary flow and a > or = 20 mmHg fall in systolic contraction pressure, n = 10) and normoxia (n = 11). For both 201Tl and MIBI, we found that under ischaemic conditions (as compared with normoxia) there was a higher initial net extraction fraction (201Tl: 0.78 +/- 0.03 vs 0.72 +/- 0.06, P = 0.006; MIBI: 0.49 +/- 0.10 vs 0.39 +/- 0.11, P = 0.03), a lower clearance rate in the 30 min following extraction (% decrease in cardiac uptake: 201Tl: 30 +/- 12 vs 47 +/- 14, P = 0.02; MIBI: 5 +/- 5 vs 13 +/- 11, P = 0.02) and a higher retention fraction at 30 min (201Tl: 0.54 +/- 0.10 vs 0.39 +/- 0.12, P = 0.004; MIBI: 0.46 +/- 0.08 vs 0.33 +/- 0.12, P = 0.01). Multivariate analyses, however, revealed that all myocardial kinetic parameters of both tracers were dependent only on coronary flow rates, without any additional significant impact of the presence of ischaemia or states of contractility or oxidative metabolism. We conclude that the myocardial fractional retention of both 201Tl and MIBI is strongly correlated with the decrease in coronary flow during ischaemia. This inverse relationship with coronary flow derives from both the flow-dependent increase in the initial myocardial extraction and the decrease in the subsequent myocardial washout of the tracers.

Publication Types:

- * Comparative Study
- * Research Support, Non-U.S. Gov't

PMID: 11105819 [PubMed - indexed for MEDLINE]

Gordon M. Harrington, Professor Emeritus
University of Northern Iowa

*uptake + retention related to Q_c
not myocardial flow
(g. mitochondria)*

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Expression and Localization of P-glycoprotein in Human Heart: Effects of Cardiomyopathy

Konrad Meissner, Bernhard Sperker, Christiane Karsten, Henriette Meyer zu Schwabedissen, Ute Seeland, Michael Böhm, Sandra Bien, Peter Dazert, Christiane Kunert-Keil, Silke Vogelgesang, Rolf Warzok, Werner Siegmund, Ingolf Cascorbi, Michael Wendt, and Hevo K. Kroemer

Institut für Pharmakologie und Peter Holtz Research Center of Pharmacology and Experimental Therapeutics (KM,B5,CK,HM25,SB,PD, CK-K,W5,CK,HKK), Klinik für Anästhesiologie (KM,MW), Institut für Pathologie, Ernst-Moritz-Arndt-Universität Greifswald (SV,RW), Greifswald, Germany, and Medizinische Klinik III, Universität des Saarlandes (US,MB), Homburg/S., Germany

SUMMARY ABC-type transport proteins, such as P-glycoprotein (P-gp), modify intracellular concentrations of many substrate compounds. They serve as functional barriers against entry of xenobiotics (e.g., in the gut or the blood-brain barrier) or contribute to drug excretion. Expression of transport proteins in the heart could be an important factor modifying cardiac concentrations of drugs known to be transported by P-gp (e.g., β -blockers, cardiac glycosides, doxorubicin). We therefore investigated the expression and localization of P-gp in human heart. Samples from 15 human hearts (left ventricle; five non-failing, five dilated cardiomyopathy, and five ischemic cardiomyopathy) were analyzed for expression of P-gp using real-time RT-PCR, immunohistochemistry, and *in situ* hybridization. Immunohistochemistry revealed expression of P-gp in endothelium of both arterioles and capillaries of all heart samples. Although P-gp mRNA was detected in all samples, its expression level was significantly reduced in patients with dilated cardiomyopathy. We describe variable expression of P-gp in human heart and its localization in the endothelial wall. Thus, intracardiac concentrations of various compounds may be modified, depending on the individual P-gp level. (*J Histochem Cytochem* 50:1351-1356, 2002)

ABC (P_{gp}) → ↓ uptake of
 cytotoxic drugs
 also involved in regulation
 of D₅, β-lactams, etc.

KEY WORDS
 P-glycoprotein
 heart
 drug transport
 cardiomyopathy

IT IS INCREASINGLY RECOGNIZED that drug transport across biomembranes is facilitated by membrane proteins. Such drug transporters belonging to the ABC (ATP-binding cassette) family can influence the intracellular concentration and hence the action of many compounds in a variety of cells and tissues (Tishler et al. 1995; Drach et al. 1996; Schinkel et al. 1997; Wijnholds et al. 1997). The initial observation of therapeutic implications resulted from chemotherapy-resistant tumor cells, which had a high expression of the ABC transporter P-glycoprotein (P-gp), leading to low intra-

cellular concentrations of cytotoxic drugs. Subsequent investigations described expression of P-gp and other transport proteins under physiological conditions in various cells (e.g., enterocytes, hepatocytes, endothelial cells of the blood-brain barrier). P-gp may serve as a functional barrier against drug entry (expression in the gut wall results in low absorption) or contribute to drug excretion (expression at the canalicular site of hepatocytes or tubule cells). Moreover, expression in endothelial cells of the blood-brain barrier protects against drug penetration into the CNS (Jette et al. 1993). Consequently, knockout mice devoid of P-gp activity have major alterations in drug disposition (enhanced absorption and high CNS concentrations of P-gp substrates; Kawahara et al. 1999; Schinkel 1997).

Expression of P-gp in humans reveals a wide inter-individual variability. Both genetic and environmental factors have been identified that contribute to this

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What is reverse distribution? mibi

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Prediction of functional recovery in acute myocardial infarction: comparison between sestamibi reverse redistribution and sestamibi/BMIPP mismatch.

Fujiwara S, Takeishi Y, Atsumi H, Yamaki M, Takahashi N, Yamaoka M, Tojo T, Tomoiike H.

First Department of Internal Medicine, Yamagata University School of Medicine, Iida-Nishi, Japan. sfujiwar@med.id.yamagata-u.ac.jp

BACKGROUND: It has been known that Tc 99m sestamibi/iodine 123 betamethylodophenylpentadecanoic (123I-BMIPP) (sestamibi/BMIPP) mismatch is an indicator of viable myocardium in acute myocardial infarction (AMI). We have reported that reverse redistribution of sestamibi in AMI indicates the patency of infarct-related artery and a preserved left ventricular function in the chronic stage. In this study we investigated the relationship between reverse redistribution of sestamibi and sestamibi/BMIPP mismatch in patients with AMI. METHODS: Twenty-three patients with AMI who received direct percutaneous transluminal coronary angioplasty underwent both BMIPP and sestamibi SPECT within 2 weeks after onset. Sestamibi images were obtained 1 hour (early) and 3 hours (delayed) after injection of sestamibi. BMIPP imaging was carried out 30 minutes after injection. The left ventricle was divided into 17 segments, and regional myocardial uptakes of the tracers in each segment were scored from 0 (normal) to 3 (no activity). A reverse redistribution pattern was defined as an increase of ≥ 1 in the regional score at the delayed images. More reduced BMIPP uptake than sestamibi uptake in each segment was determined as sestamibi/BMIPP mismatch. Contrast left ventriculography was performed soon after revascularization and repeated 1 month later. RESULTS: Of 15 patients with sestamibi reverse redistribution, sestamibi/BMIPP mismatch was observed in 14 patients (93%), whereas mismatch was seen in only one of seven patients (14%) without reverse redistribution ($p < 0.01$). In patients with sestamibi reverse redistribution, regional scores of BMIPP agreed with those of early and delayed images of sestamibi in 51 segments (46%) and in 92 segments (83%), respectively. In the chronic stage, both regional wall motion and left ventricular ejection fraction improved in patients with sestamibi reverse redistribution (wall motion score: 6.7 ± 2.4 vs 2.7 ± 2.1 , $p < 0.01$; ejection fraction: $56\% \pm$

*Left ventricle of septum -
 you can get some info E
 delayed MIBI images
 Henry Lagarto (Lacation
 S. Brice)*

2 weeks p AMI

= WASH IN

*Washin p PCA = good
 marker of recovered
 myocardium*

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mibi 5min and 2hr

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Washout and redistribution between immediate and two-hour myocardial images using technetium-99m sestamibi.

Richter WS, Cordes M, Calder D, Eichstaedt H, Felix R.

Universitätsklinikum Rudolf Virchow, Freie Universität Berlin, Germany.

The aim of this study was to assess whether a clinically relevant change in myocardial sestamibi activity could be documented within the first 120 min following injection (p.i.). In 17 patients planar anterior imaging of the heart was performed 5 min and 120 min p.i. During this time interval, mean decay-corrected myocardial activity declined to 77.9% +/- 9.7% after stress and to 85.7% +/- 7.9% after injection at rest ($P < 0.05$). In 19 patients with angiographically documented coronary artery disease, single-photon emission tomography was performed 5 min and 120 min after injection at maximum stress. For analysis, sestamibi activity was scored semiquantitatively in six left ventricular segments. Furthermore, sestamibi uptake was assessed quantitatively using a circumferential profile method. In 35 of 114 segments the score improved within 120 min p.i. (early fill-in); in these segments relative sestamibi activity rose from 69.9% +/- 22.5% to 74.5% +/- 20.8% ($P < 0.01$). In five patients this early fill-in was the only sign of exercise-induced hypoperfusion. In 7 of 114 segments the score deteriorated 120 min p.i. (early tracer washout); in these segments relative sestamibi activity declined from 85.6% +/- 9.9% to 80.1% +/- 10.7% ($P < 0.02$). In three of four patients with early tracer washout the corresponding coronary artery was significantly narrowed. In conclusion, a global myocardial sestamibi washout was registered within the first 120 min after injection. A fill-in of initial defects as well as an early tracer loss could be detected in a relevant number of patients with chronic coronary artery disease during the first 2 h p.i. (ABSTRACT TRUNCATED AT 250 WORDS)

1. wash in
 $\frac{5}{14} = 26.32$ wash in only
 sig. of segs
 75% washout - manual activity

Publication Types:

* Comparative Study

PMID: 7698155 [PubMed - indexed for MEDLINE]

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Comparison between 201Tl and 99mTc sestamibi uptake during adenosine-induced vasodilation as a function of coronary stenosis severity.

Glover DK, Ruiz M, Edwards NC, Cunningham M, Simanis JP, Smith WH, Watson DD, Beller GA.

Department of Medicine, University of Virginia, Charlottesville 22908.

BACKGROUND: Myocardial uptake of either 201Tl or 99mTc-sestamibi (sestamibi) is known to plateau at high coronary flow rates. However, few direct comparisons have been made between these tracers to determine what effect differences in the uptake plateau for the two tracers may have on the detection of coronary stenoses of various severities. **METHODS AND RESULTS:** Twenty-two dogs were instrumented with flow transducers on the left anterior descending (LAD) and circumflex (LCx) arteries. In 6 nonstenotic dogs, adenosine was infused directly into the LAD, whereas 16 dogs with either critical (n = 7) or mild (n = 9) LAD stenoses received an intravenous infusion. At peak flow, 201Tl (0.5 mCi), sestamibi (5 to 8 mCi), and radiolabeled microspheres were injected simultaneously. Five minutes later, dogs were killed, and ex vivo imaging of heart slices and gamma-well counting of multiple myocardial samples was performed. Neither 201Tl nor sestamibi uptake increased in direct proportion to flow. In the 6 nonstenotic dogs, a fivefold increase in LAD flow increased 201Tl and sestamibi uptake by only 202 +/- 6% and 138 +/- 4%, respectively (P < .0001). In the dogs with critical stenosis, the ratios of stenotic to normal activity by well counting for 201Tl (0.37 +/- 0.05) and sestamibi (0.53 +/- 0.06) underestimated the microsphere-determined flow disparity (0.17 +/- 0.03) (P < .005), but the degree of underestimation was greater for sestamibi (P = .001). Similarly, in the dogs with mild stenosis, the stenotic-to-normal ratio for 201Tl (0.62 +/- 0.04) approximated the flow ratio (0.43 +/- 0.04) better than sestamibi (0.79 +/- 0.03) (P < .0001). Sestamibi defects, however, were visually identifiable on the images of the myocardial slices. Gy image

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Myocardial technetium-99m-tetrofosmin uptake during adenosine-induced hyperemia in dogs with either a critical or mild coronary stenosis: comparison to thallium-201 and regional blood flow. [J Nucl Med. 1995]

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quantification, sestamibi defect magnitude (LAD-to-LCx count ratio) in the critical stenosis group (0.62 ± 0.05) was significantly less than in the mild stenosis group (0.80 ± 0.02) ($P < .01$). CONCLUSIONS: Thus, with adenosine-induced hyperemic flow, both 201Tl and sestamibi significantly underestimated the magnitude of the flow disparity between stenotic and normal perfusion beds. The degree of underestimation was greater for sestamibi. The clinical implication of these experimental findings for vasodilator perfusion imaging remains to be determined, since factors such as greater redistribution and scatter with 201Tl could offset its advantages.

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Pulmonary Uptake of Technetium-99m-Sestamibi Induced by Dipyridamole-Based Stress or Exercise

Gilbert A. Hurwitz, Samia K. Ghali, Mariwan Husni, Piotr J. Slomka, Adel G. Mattar, Robert H. Reid and Neville M. Lefcove
Departments of Diagnostic Radiology, Nuclear Medicine and Medicine, University of Western Ontario; and Department of Nuclear Medicine, Victoria Hospital, London, Ontario, Canada

On poststress images with ^{99m}Tc -sestamibi (MIBI), increased lung uptake of the radiotracer may reflect severe or multivessel coronary artery disease. **Methods:** We measured pulmonary/myocardial ratios of MIBI at standardized times on immediate poststress acquisitions and on delayed tomographic acquisitions. In 1500 sequential patients referred for rest and stress myocardial tomography, ancillary planar images were obtained 4 min postinjection at peak stress with exercise, either alone (exercise, $n = 674$), or after intravenous dipyridamole (dipyridamole, $n = 826$). **Results:** Based on 95% confidence limits in the angiographic normals, high values for immediate acquisitions were found in 17% of dipyridamole studies and 15% of exercise studies. High values for delayed acquisitions were found in 10% of dipyridamole studies and 9% of exercise studies. For both stress modes, increased values were related ($p < 0.001$) to ischemic perfusion defects for immediate images, to fixed defects for delayed images, and to ventricular dilation in both cases. By logistic regression analysis, body weight and history of infarction were also minor independent determinants ($p < 0.01$) of delayed acquisitions. In a subset of 250 cases with angiographic correlation (183 with dipyridamole; 67 with exercise), immediate lung uptake was highly correlated with ventricular dysfunction and with coronary stenoses ($p < 0.0001$). Relationships were similar to those in a historic control series imaged with ^{201}Tl . Values for delayed poststress images, and for corresponding rest images, showed strong relationships to ventricular dysfunction but not to stenosis severity. **Conclusion:** The relationships of immediate lung uptake to scintigraphic and angiographic disease patterns suggest its possible diagnostic use as an indicator of stress-induced ventricular decompression.

Key Words: technetium-99m-sestamibi; lung uptake; tomographic acquisitions; dipyridamole

J Nucl Med 1998; 39:339-345

In using technetium-based agents for myocardial imaging (1,2), a potential drawback is the decreased value of pulmonary uptake of the perfusion agent. With ^{201}Tl , the classic radionuclide used for this purpose, lung uptake can be assessed as an ancillary aspect of interpretation of planar or tomographic imaging. Increased poststress lung uptake of ^{201}Tl has considerable diagnostic value because it correlates with multivessel or severe coronary artery disease (3-5). Major prognostic value has been attributed to this ancillary imaging sign (5-8). The diagnostic relevance of stress-induced lung uptake of ^{201}Tl has been shown after a variety of stress modalities (9,10), but relationships to gender, peak exercise heart rate and other factors may modify its interpretation (4,5). Although ^{99m}Tc -sestamibi (MIBI) has been in widespread use for several years, there is only limited information (11-15) concerning the potential value of pulmonary uptake with it. This probably derives from the standard imaging protocols with MIBI in which

imaging is usually not performed until at least 30 min after stress injection.

Published studies leave unanswered questions about the usefulness of lung uptake measurements with MIBI. On conventional MIBI images obtained 1 hr after stress, the value of lung uptake as an ancillary diagnostic sign has been reported as absent (14), reduced in comparison to ^{201}Tl (12,13) or possibly as helpful as those of ^{201}Tl (11). Most previous studies have focused on exercise rather than on pharmacological stress. Recently, Giubbini et al. (15) found that lung uptake on images acquired 1 hr after ergometric exercise correlated well with left ventricular dysfunction but not with the number of stenosed coronary arteries.

A few studies (12,13) have suggested that lung uptake of MIBI may be a more useful sign of disease when measured on immediate poststress images compared to standard acquisitions at 1 hr after injection. We reviewed the routine use of early poststress MIBI images (16) and evaluated images performed after dipyridamole-based tests as well as after ergometric stress.

MATERIALS AND METHODS

Sequential MIBI Imaging Series

From April 1992 to September 1993, 1500 sequential referrals were made to the nuclear medicine department at Victoria Hospital for diagnostic stress myocardial scintigraphy. These studies involved 1445 patients (evaluations were performed on two separate occasions in 53 patients and on three occasions in 1 patient) and were ordered by referring physicians for the usual clinical indications (16). Tomographic imaging with MIBI was used as the standard laboratory procedure to assess myocardial perfusion. Starting in April 1992, all patients had ancillary images taken starting at 4 min after peak stress with a mobile camera situated beside the stress table (13,16). These images were acquired in the left anterior oblique 40° projection for 2 min in the electrocardiogram (ECG)-gated mode with 16 frames synchronized to the R-wave. As part of routine image interpretation, these images were displayed in cinematic mode and used for visual rating of ventricular contractile function including left ventricular size (17). With all frames added together for better count statistics, these images also were used to assess abdominal background (16). Although relative lung uptake was observed on these images, quantitation of lung uptake was not included routinely.

Routine MIBI Perfusion Studies

Patients were assigned to supine bicycle ergometry stress alone if a brief clinical assessment suggested that would allow them to reach a diagnostic stress level (16,18). If exercise capacity was considered limited, stress was performed with vasodilatation with dipyridamole combined with either bicycle exercise or repeated isometric exercise, as appropriate. In this series, 674 patients (45% of the 1500 patients) were studied with exercise stress alone, and 826 patients (55%) were studied with dipyridamole-based tests. At peak exercise, MIBI was injected in a dose of 12 MBq/kg body weight. To ensure MIBI uptake by the myocardium (19), exercise

Received Dec. 12, 1996; revision accepted Apr. 1, 1997.

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part 7

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Noncardiac findings on dual-isotope myocardial perfusion SPECT.

Williams KA, Hill KA, Sheridan CM.

Department of Medicine, University of Chicago, 5758 S. Maryland Avenue, MC9025, Chicago, IL 60637, USA. kwilliam@medicine.bsd.uchicago.edu

BACKGROUND: This study examined the frequency of reporting noncardiac findings (NCFs), such as malignancies from inspection of raw projection images with dual-isotope single photon emission computed tomography (SPECT) perfusion imaging, which could potentially be of greater clinical importance than myocardial perfusion imaging alone. Dual-isotope (ie, rest thallium 201 and stress technetium 99m sestamibi [MIBI] or Tc-99m tetrofosmin [TET]) SPECT myocardial perfusion imaging combines multipotential tracers for noncardiac purposes (Tl-201 for renal or splenic imaging, inflammation, or lymphoma and MIBI or TET for hepatobiliary imaging and detecting increased mitochondrial number or activity in neoplastic processes). These images are optimally interpreted with cinematic inspection of the raw projection data, but this may not be practiced uniformly in every laboratory. **METHODS AND RESULTS:** We reviewed 12,526 computer-generated text reports of dual-isotope perfusion SPECT studies from a 6-year period for NCFs. NCFs were categorized by organ and by probability of malignancy: high (eg, focal breast or lung uptake of MIBI or TET), intermediate (eg, lymph node uptake or thyroid abnormalities), or low (eg, filling defects in liver, kidney, spleen, or gall bladder; ascites; or pleural effusions). Confirmatory imaging studies or clinical confirmation for each NCF was sought. There were a total of 207 NCFs identified in 180 reports (1.7% of reports, ranging from 0% to 2.8% of reports of individual interpreters). Of these, 107 NCFs were unsuspected before SPECT; 24% were considered at high probability for malignancy, and 24% were considered intermediate in likelihood of malignancy. Follow-up data were available for 178 NCFs, confirming 88% of these findings, including 82% of breast foci, 62% of lung foci, 86% of hepatobiliary/spleen abnormalities, and 94% of renal abnormalities. The probability of malignancy was highest (82%) in breast or lung foci in which uptake of both Tl-201 and the Tc-99m-labeled agent was present. **CONCLUSIONS:** In patients referred for evaluation of myocardial perfusion, NCFs are unusual and require systematic and careful inspection of projection images for their detection. With Tl-201, TET, MIBI, or dual-isotope imaging, detecting and reporting NCFs may occasionally result in life-saving early cancer identification.

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♦ UPDATE ON THYMUS AND THYMIC DISORDERS ♦

Functional imaging of thymic disorders

Secondo Lastoria, Giovannella Palmieri¹, Pietro Muto and Gaetano Lombardi¹

Human thymomas are rare tumours which usually develop in the chest. The diagnosis via guided biopsy, the evaluation of the extent of the tumour and its boundaries with adjacent organs, the choice of the appropriate therapeutic option, and the assessment of response to treatment are usually made with computed tomography (CT) alone or in combination with magnetic resonance imaging (MRI). More recently, radiopharmaceuticals and nuclear medicine procedures have been used increasingly in the imaging and functional characterization of benign and malignant thymic disorders. Two groups of radiopharmaceuticals have been used. The first includes several oncotrophic tracers, such as ²⁰¹Tl-chloride, ^{99m}Tc-sestamibi and ¹⁸F-fluorodeoxyglucose, which are significantly concentrated in thymic tumours. Their uptake correlates with tumour grades and cellularity. The second class includes two radioligands: [¹¹¹In-DTPA-D-Phe¹]-octreotide (DTPA, diethylenetriamine penta-acetic acid) and [¹¹¹In-DTPA-Arg¹]-substance P, which bind to specific receptors. [¹¹¹In-DTPA-Arg¹]-substance P binds to its receptors that are largely expressed in the thymus of patients with autoimmune diseases. [¹¹¹In-DTPA-D-Phe¹]-octreotide recognizes the somatostatin receptor subtype 2. In patients with active disease investigated in our institution [¹¹¹In-DTPA-D-Phe¹]-octreotide has been shown to concentrate in the majority of thymoma deposits. Conversely, it is not concentrated in adult patients with benign lymphofollicular thymic hyperplasia. This finding has had a significant impact on the management of patients with myasthenia gravis as it differentiates early-stage thymoma from benign hyperplasia, unlike CT and MRI, which often fail to distinguish between the two. In addition to its role in diagnostic imaging, somatostatin receptor scintigraphy also enables us to select patients with advanced or metastatic thymoma unresponsive to conventional therapies, who might benefit from a somatostatin analogue-based treatment, serving thus as a link between diagnosis and therapy. In this article, we discuss and analyse the results of functional imaging with different radiopharmaceuticals, primarily those that we have obtained with [¹¹¹In-DTPA-D-Phe¹]-octreotide.

Key words: [¹¹¹In-DTPA-D-Phe¹]-octreotide; radiolabelled peptides; somatostatin receptor scintigraphy; thymic benign hyperplasia; thymic tumours.

Ann Med 1999; 31: Suppl 2: 63-69.

Introduction

Human thymomas are rare tumours which usually develop in the anterior mediastinum and often infiltrate

adjacent thoracic organs, while they rarely metastasize outside the chest (1, 2). Thymomas are epithelial tumours frequently associated with an exuberant lymphoid component, composed of immature cortical thymocytes proliferating at rates comparable to those seen in fetal thymuses (3, 4). Previous histological classifications describe thymomas as benign or malignant, but they should be more correctly divided into invasive and noninvasive tumours to define the behaviour of the disease. At present, the most commonly used classification includes the following

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Articles

Myocardial Uptake of ^{99m}Tc -Tetrofosmin, Sestamibi, and ^{201}Tl in a Model of Acute Coronary ReperfusionNorio Takahashi, MD; Christopher P. Reinhardt, PhD;
Robin Marcel; Jeffrey A. Leppo, MD

the Myocardial Isotope Research Lab, Departments of Nuclear Medicine and Medicine (Division of Cardiology), University of Massachusetts Medical Center, Worcester.

Correspondence to Norio Takahashi, MD, Department of Nuclear Medicine, UMass Medical Center, 55 Lake Ave N, Worcester, MA 01655-0243.

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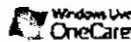
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This includes a paper on how a single acquisition (one dynamic) can yield the magical rest-stress images. Gee, I wonder how Kathy will deal with this in the future. Finally, the research paper on soy shows similar results with my earlier work. One true marker of correctly done research is reproducibility - something most High School students grasp, since they can never seem to reproduce results from their textbooks.

CASE REPORT

Annals of Nuclear Medicine Vol. 18, No. 6, 547-549, 2004

Brown adipose tissue: Evaluation with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi dual-tracer SPECTTakahiro HIGUCHI,* Seigo KINUYA,** Junichi TAKI,** Kenichi NAKAJIMA,**
Masatoshi IKEDA,*** Masanobu NAMURA*** and Norihisa TONAMI**

*Department of Kanazawa PET Center, Kanazawa Cardiovascular Hospital

**Department of Biomedical Medicine, Kanazawa University Graduate School of Medical Sciences

***Department of Cardiology, Kanazawa Cardiovascular Hospital

Brown adipose tissue is one kind of adipose tissue and regulates body temperature and balance of energy via non-shivering thermogenesis. The authors present a case that strongly suggested the presence of activated brown adipose tissue in the neck, shoulders and axillary space by increased ^{18}F -FDG uptake. $^{99\text{m}}\text{Tc}$ -sestamibi and ^{201}Tl dual-tracer SPECT study showed increased $^{99\text{m}}\text{Tc}$ -sestamibi uptake and non-increased ^{201}Tl uptake in the corresponding ^{18}F -FDG uptake sites. Brown adipose tissue has dense mitochondria in the cells, which play an important role in thermogenesis. $^{99\text{m}}\text{Tc}$ -sestamibi uptake and retention depend on the mitochondrial activity but ^{201}Tl uptake does not. Therefore, the activity of mitochondria in activated brown adipose tissue may explain the discrepant uptake between $^{99\text{m}}\text{Tc}$ -sestamibi and ^{201}Tl .

Key words: brown adipose tissue, ^{18}F -FDG, ^{201}Tl , $^{99\text{m}}\text{Tc}$ -MIBI, PET

INTRODUCTION

BROWN ADIPOSE TISSUE has a unique ability to generate heat with non-shivering process for thermoregulation and utilization of excess caloric intake.¹ The heat generation is related to the metabolism of the mitochondria that have a specific carrier called uncoupling protein. It produces heat without subsequent production of ATP.^{2,3} The tissue is located mainly in the supraclavicular area, comprising up to 5% of body weight in newborns. It gradually diminishes with age but persistently exists in some adult humans.¹

Recently some studies have reported the uptake of ^{18}F -FDG,⁴⁻⁷ ^{123}I -MIBG⁸ and $^{99\text{m}}\text{Tc}$ -tetrofosmin⁹ in bilateral neck and shoulders indicating the presence of activated adipose tissue. We report findings with dual tracer SPECT with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi in a patient showing ^{18}F -FDG uptake in bilateral neck and shoulder fat tissue

leadings to suspect the presence of activated brown adipose tissue and discuss the mechanism of these tracer uptake.

CASE REPORT

A 25-year-old woman underwent total thyroidectomy and cervical lymph node dissection for papillary adenocarcinoma. Because the increase of serum thyroglobulin persisted after the operation, ^{18}F -FDG PET was performed for the survey of metastatic lesions. Tomographic data acquisition was performed 90 minutes after intravenous injection of 370 MBq of ^{18}F -FDG with a PET scanner (Accel; Siemens). PET images were fused with those of X-ray CT using fusion software (eNTEGRA; General Electric Medical Systems). PET image delineated intense FDG accumulation bilaterally in the neck, supraclavicular region, and axillae (Fig. 1A, B). Fusion images confirmed that the uptake was located in the fatty tissue, not in the muscle (Fig. 1C). These findings strongly suggested the presence of activated brown adipose tissue, as verified in previous reports.⁴⁻⁷ Dual-tracer SPECT with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi was also performed at 30

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E-mail: higuchi@med.kanazawa-u.ac.jp

A000267

Fleming Motion to Vacate - Appendix

November 4, 2015-21

images with 4-dimensional MSPECT, and mean values were generated for each image set.

Results: Relative Myocardial Counts (% Maximum).

	FBP	IT	IT + AC	IT + AC + SC
All (n=42)				
Total	76.6 ± 4.8	76.5 ± 4.8	80.5 ± 3.2***	79.2 ± 3.6*
LAD	76.6 ± 6.7	77.4 ± 5.2	77.1 ± 4.0	75.8 ± 4.4
CPX	77.7 ± 6.7	74.8 ± 7.3	84.5 ± 5.0***	84.8 ± 5.3***
RCA	74.2 ± 8.4	74.8 ± 8.7	83.5 ± 5.1***	81.3 ± 5.6**
Men (n=18)				
Total	75.8 ± 4.3	73.7 ± 3.9	80.3 ± 3.1**	78.1 ± 3.6*
LAD	76.8 ± 4.2	76.7 ± 4.7	77.5 ± 3.9	76.0 ± 4.5
CPX	78.0 ± 6.5	73.9 ± 6.6	85.2 ± 5.0**	85.9 ± 4.8**
RCA	70.3 ± 8.6	70.4 ± 8.8	81.6 ± 6.0**	79.8 ± 6.5**
Women (n=24)				
Total	77.3 ± 4.8	77.1 ± 5.3	80.8 ± 3.4*	79.4 ± 3.8
LAD	76.4 ± 5.7	76.5 ± 5.5	76.9 ± 4.2	75.7 ± 4.4
CPX	77.5 ± 6.9	75.4 ± 7.9	83.9 ± 4.9*	84.0 ± 5.6**
RCA	77.0 ± 7.2	78.0 ± 7.1	84.9 ± 3.8**	82.5 ± 4.7**

*p < 0.05 vs FBP and IT; **p < 0.005 vs FBP and IT; ***p < 0.0001 vs FBP and IT; *p < 0.05 vs FBP and IT; **p < 0.0002 vs FBP and IT; ***p < 0.00002 vs FBP and IT; *p < 0.05 vs IT, p = 0.05 vs FBP; +p < 0.05 vs FBP, p = 0.055 vs IT.

For total counts and for each vascular distribution, raw AC and AC+SC myocardial image counts were significantly increased (up to 7-fold greater on the IT+AC images and 8-fold greater on the IT+AC+SC images) than on conventional FBP images.

Conclusions: Application of AC or AC+SC significantly alters both normalized and raw count distributions on SPECT myocardial perfusion images, indicating that attenuation correction with or without scatter correction must be considered when comparing individual image data to normal databases for both men and women. Moreover, the increase in myocardial image counts with AC and AC+SC suggests that these reconstruction techniques may benefit image quality.

15.31

MYOCARDIAL PERFUSION SPECT: REST AND STRESS IN ONE ACQUISITION

BE Backes,¹ FA Verburg,² MW Konijnsberg,³ JF Verzijlbergen⁴

¹St Antonius Hospital, Nieuwegein, Netherlands, ²Universitair Ziekenhuis, Würzburg, Germany, ³Covidien BV, Petten, Netherlands

Background: Simultaneous Dual Isotope (SDI) acquisition of ²⁰¹Tl rest/^{99m}Tc sestamibi stress-myocardial perfusion single-photon emission computed tomography (MPS) is a desirable new procedure in nuclear cardiology. In this protocol ²⁰¹Tl is injected at rest but imaging is performed not earlier than after exercise. Therefore one must be convinced that throughout exercise ²⁰¹Tl remains distributed in an identical pattern as at rest. Before SDI can be applied clinically, ²⁰¹Tl rest MPS before and after an exercise test need to be compared for equality. This study assesses the variation in washout of Thallium in normally perfused and ischemic myocardium subjected to exercise.

Methods: In 102 patients ²⁰¹Tl was injected in rest. Rest ²⁰¹Tl MPS was performed, followed by an upright bicycle exercise-test, without injection of any tracer. Subsequently post-stress ²⁰¹Tl imaging was performed (see figure). All images were corrected for attenuation and decay. Quantitative analysis of mean counts-per-pixel for each segment in a 17-segment model was done using MunichHeart. Differences between rest and post-stress ²⁰¹Tl MPS were calculated. Normal segments were compared to ischemic segments. Visual analysis was performed by two independent observers scoring the 17 segments on a scale of 0-4.

Results: Overall global difference between rest ²⁰¹Tl and post-stress ²⁰¹Tl MPS was 15.4% (± 0.7% s.e.m.). Normal (N=66) and ischemic (N=36) patients demonstrated 16.2% (± 0.7%) and 14.0% (± 1.4%) (p=0.17) washout respectively. Quantitative analysis demonstrated no significant segmental differences between normal and ischemic myocardium. Visual assessment by two independent observers revealed a significant difference between rest ²⁰¹Tl and stress ²⁰¹Tl MPS in only one patient. The clinical diagnosis in this patient would have altered from ischemia only to infarct with ischemia.

Conclusion: ²⁰¹Tl post-stress MPS demonstrates significant redistribution Thallium. This washout is global over the myocardium. The post-stress ²⁰¹Tl MPS is a reliable reflection of the rest perfusion, even in ischemic

segments. SDI acquisition of ²⁰¹Tl rest/^{99m}Tc sestamibi stress-MPS is clinically applicable.



15.32

DIAGNOSTIC ACCURACY OF HYBRID CARDIAC SPECT/CT F-ATTENUATION CORRECTION OF STRESS MYOCARDIAL PERFUSION IMAGING IN OBESE COMPARED TO NORMAL WEIGHT PATIENT

JR Corbett, JM Cahill, JN Kritzman, JJ Meden, EP Ficaro

University of Michigan, Ann Arbor, MI

Background: The purpose of this study was to evaluate the diagnostic accuracy of computed tomography (CT)-based attenuation corrected (AC) single-photon emission computed tomography (SPECT) myocardial perfusion imaging compared to uncorrected SPECT (NC) in consecutive obese (body mass index [BMI] > 30) compared to normal weight patients (pts) with angiographic correlates.

Methods: We studied 234 pts with recent coronary angiographic correlates. This study included 101 pts with BMI < 30 (normal group) and 133 pts with BMI > 30 (obese group). The mean weight of normal pts was 75.9 ± 13.0 Kg (range 46.4-104.5 Kg) and mean weight of the obese group was 107.8 ± 19.7 Kg (range 63.2-181.8 Kg); BMI averaged 25.5 ± 3.2 (range 16.5-29.8) in the normal group and 37.1 ± 6.97 (range 30.1-66.6) in the obese group. Imaging was performed using Siemens SYMBIA-T6 SPECT-CT imaging systems (Siemens Medical Solutions, Hoffman Estates, IL) and a stress Tc-99m sestamibi protocol. Breathhold CT acquisitions were acquired at end tidal expiration, 5-7 sec, acquisition time. SPECT images were reconstructed for attenuation correction (including scatter correction and resolution recovery) using manufacturers' software without modification. Perfusion defects were assessed by scoring the severity and extent of perfusion defects in each of the three coronary artery distributions using the standard 17-segment model. For statistical purposes, p < 0.05 was considered significant.

Results: With AC sensitivity increased from 86% to 94% in normal weight pts and from 76% to 94% in obese pts (p < 0.05). Specificity increased from 81% to 94% in normal weight pts and from 48% to 83% in obese pts (p < 0.05). Accuracy increased from 85% to 94% in normal weight pts and from 69% to 91% in obese pts (p < 0.05). Increases in sensitivity, specificity and accuracy all occurred. These improvements were larger and all were significant in the obese patient group. The normal weight group also demonstrated significant improvements in sensitivity and accuracy with a trend to increased specificity.

Conclusion: CT-based attenuation correction significantly improves the diagnostic accuracy of MPI SPECT in normal weight and obese patients, but the improvements are greater in obese patients. Although significantly improved, specificity is still significantly reduced in obese compared to normal weight patients.

15.33

DIAGNOSTIC ACCURACY OF HYBRID SPECT/CT FOR ATTENUATION CORRECTION OF STRESS MYOCARDIAL PERFUSION IMAGING IN WOMEN COMPARED TO MEN

JR Corbett, JM Cahill, JN Kritzman, JJ Meden, EP Ficaro

University of Michigan, Ann Arbor, MI

Objective: The objective of this study was to evaluate the diagnostic accuracy of computed tomography (CT)-based attenuation corrected (AC) single-photon emission computed tomography (SPECT) myocardial perfusion imaging compared to uncorrected SPECT (NC) in female compared to male patients (pts) with angiographic correlates.

Methods: We studied 237 pts with recent coronary angiographic correlates including 143 consecutive male (mean age 61.2 ± 10.6 and mean weight 98.9 ± 21.4 Kg (range 54.5-174.1 Kg)) and 94 consecutive female patients (mean age 62.5 ± 12.8 and mean weight 86.8 ± 24.3 Kg (range 46.4-181.8 Kg)). Imaging was performed using Siemens SYMBIA-T6 SPECT-CT imaging systems (Siemens Medical Solutions, Hoffman Estates, IL) and a stress Tc-99m sestamibi protocol. Breathhold CT acquisitions were acquired at end tidal expiration, 5-7 sec, acquisition time. SPECT images were reconstructed for attenuation correction (including scatter correction and

Effectiveness of a soy-based compared with a tradi...[Nutrition. 2007 Jul-Aug] - PubMed Result

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Note: Performing your original search, *soy AND weight loss*, in PubMed will retrieve **113** records.

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☐ 1: Nutrition. 2007 Jul-Aug;23(7-8):551-6. Epub 2007 Jun 15.

ELSEVIER Links

Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults.

Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW.

School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan, Republic of China.

OBJECTIVE: This study investigated the effects of a soy-based low-calorie diet on weight control, body composition, and blood lipid profiles compared with a traditional low-calorie diet. **METHODS:** Thirty obese adults (mean body mass index 29-30 kg/m²) were randomized to two groups. The soy-based low-calorie group consumed soy protein as the only protein source, and the traditional low-calorie group consumed two-thirds animal protein and the rest plant protein in a 1200 kcal/d diet for 8 wk. A diet record was kept everyday throughout the study. Food intake was analyzed before and after the study. Anthropometric data were acquired every week, and biochemical data from before and after the 8-wk experiment were compared. **RESULTS:** Body weight, body mass index, body fat percentage, and waist circumference significantly decreased in both groups ($P < 0.05$). The decrease in body fat percentage in the soy group (2.2%, 95% confidence interval 1.6-2.8) was greater than that in the traditional group (1.4%, 95% confidence interval -0.1 to 2.8). Serum total cholesterol concentrations, low-density lipoprotein cholesterol concentrations, and liver function parameters decreased in the soy-based group and were significantly different from measurements in the traditional group ($P < 0.05$). No significant change in serum triacylglycerol levels, serum high-density lipoprotein cholesterol levels, and fasting glucose levels was found in the soy or traditional group. **CONCLUSION:** Soy-based low-calorie diets significantly decreased serum total cholesterol and low-density lipoprotein cholesterol concentrations and had a greater effect on reducing body fat percentage than traditional low-calorie diets. Thus, soy-based diets have health benefits in reducing weight and blood lipids.

PMID: 17574819 [PubMed - indexed for MEDLINE]

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Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. [Am J Clin Nutr. 2005]

Supplementation with soy protein-rich foods does not enhance weight loss. [J Am Diet Assoc. 2007]

Beef and soy-based food supplements differentially affect serum lipoprotein-lipid profiles because of changes in carbohydrate intake and novel nutrient intake ratios in older men who resist metabolism. 2005]

Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. [Nutrition. 2003]

Effect of a high-protein, energy-restricted diet on body composition, glycemic control, and lipid concentrations in overweight and obese hyperinsulinemic men and women. [Am J Clin Nutr. 2003]

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FW: a published paper documenting benefit of 4 minute and 60 minute post stress sestamibi

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 2/24/09 2:56 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)



1 attachment



4 minuts ...pdf (1189.4 KB)

> From: gordon.harrington@uni.edu
> To: rmfmd7@hotmail.com
> Subject: Fwd: a published paper documenting benefit of 4 minute and 60 minute post stress sestamibi
> Date: Mon, 23 Feb 2009 23:14:17 -0600

>
>
> ----- Forwarded Message -----

>
> Subject: a published paper documenting benefit of 4 minute and 60
> minute post stress sestamibi
> Date: Wednesday 19 September 2007
> From: RM Fleming <rmfmd7@hotmail.com>
> To: Mike Hansen PD corrected <mike_hansen@fd.org>

>
> Dear Mike, Let me know when we can talk to review the images I have.
> Please let me know if you received the Calkins letter. The attached
> article (published paper) shows benefit of 4 minute planar and 60
> minute SPECT imaging of sestamibi following 'stress'.

>
> Yours,
>
> Dr. Fleming

Dr. Jay

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Mon 3/09/09 12:42 PM

To: RM Fleming (rmfmd7@hotmail.com)

I am Fed Ex'ing a number of materials out to Dr. Jay today. Below is what I plan on sending to him. Is there anything else that I should send right now? (e.g. power points?) I am not sending the patient images yet. I need to speak to you first before they go to him.

1. Maublant article
2. Li article (I do not have the full Crane article yet but will send it to him when I get it)
3. Your email to Sanzone setting out the 2002 protocol
4. Your Feb 11, 2008 article "Using Multiple Images post-stress . . ."
5. Your article "Angiology"
6. The article going in some Journal entitled: "The Evolution of Nuclear Cardiology"
7. Pages 127-33 of Stop Inflammation Now! (to show the 2002 protocol "carved in stone" (my words not yours))

Looking for your continued input, Mike Hansen

From: rmfmd7@gmail.com
Subject: sestamibi and Heart to Lung imaging
Date: March 11, 2009 1:17:48 PM PDT
To: mike_hansen@fd.org

Mike,

I cannot find the request by Ryberg. The following articles apply to Heat to Lung imaging which is apparently over the head of McKusick.

- Pace L, Catalano L, Del Vecchio S, et al. Washout of [99mTc] sestamibi in predicting response to chemotherapy in patients with multiple myeloma. Q J Nucl Med Mol Imaging 2005;49:281-5.
- Hurwitz GA, Ghali SK, Husni M, et al. Pulmonary uptake of Technetium-99m-Sestamibi induced by dipyridamole-based stress or exercise. J Nucl Med 1998;39:339-45.

[This is the one (above) that got the protocol initiated at the VA Hospital in Des Moines.] It really doesn't matter what you bill today, it's reimbursed at the same rate so it doesn't matter how people would code it today!!!!!!!!!!!!!!!!!!!!]

- Hurwitz GA, Fox SP, Driedger AA, Willems C, Powe JE. Pulmonary uptake of sestamibi on early post-stress images: angiographic relationships, incidence and kinetics. Nucl Med Commun 1993;14;15-22. .
- Saha M, Forrest TF, Brown KA. Lung uptake of technetium-99m-sestamibi: relation to clinical, exercise, hemodynamic, and left ventricular function variables. J Nucl Cardiol 1994;1:52-6.
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- Sugiura T, Takase H, Toriyama T, et al. Usefulness of Tc-99m

methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8.

➤ Kumita S, Seino Y, Cho K, et al. Assessment of myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison with normal control. *Ann Nucl Med* 2002;16:237-42.

➤ Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. *J Nucl Cardiol* 2007;14:215-20.

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➤ Ikawa M, Kawai Y, Arakawa K, et al. Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of 99mTc-MIBI washout and 123I-BMIPP/99mTc-MIBI mismatch. *Mitochondrion* 2007;7:164-70.

➤ Meissner K, Sperker B, Karsten C, et al. Expression and localization of P-glycoprotein in Human Heart: Effects of Cardiomyopathy. *J Histochem Cytochem* 2002;50:1351-6.

➤ Fukushima K, Momose M, Kondo C, et al. Myocardial kinetics of (201) Thallium, (99m) Tc-tetrofosmin, and (99m) Tc-sestamibi in an acute ischemia-reperfusion model using isolated rat heart. *Ann Nucl Med* 2007;21:267-73.

➤ VanBrocklin HF, Hanrahan SM, Enas JD, et al. Mitochondrial avid radioprobes. Preparation and evaluation of 7'(Z)-[125I]iodorotenone and 7'(Z)-[125I]iodorotenol. *Nucl Med Biol* 2007;34:109-16.

➤ Tanaka R, Nakamura T, Chiba S, et al. Clinical implication of reverse redistribution on 99mTc-sestamibi images for evaluating ischemic heart disease. *Ann Nucl Med* 2006;20:349-56.

➤ Liu Z, Johnson G 3rd, Beju D, Okada RD. Detection of myocardial viability in ischemic-reperfused rat hearts by Tc-99m sestamibi

kinetics. J Nucl Cardiol 2001;8:677-86.

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- Takahashi N, Reinhardt CP, Marcel R, Leppo JA. Myocardial uptake of 99m Tc-tetrofosmin, Sestamibi, and 201 Tl in a model of acute coronary reperfusion. Circulation 1996;94:2605-13.

Dr. Fleming

RE: soy numbers

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wcd 3/18/09 4:11 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

Everything you need to know is right up front in the abstract.

I would love to know if McKusick even knows of Blumgarts work since it originated out of the same hospital according to what I have seen. (Boston Mass General).

1) Maublant. abstract, line 8 ""washout curves were, respectively, of 28 minutes" [in other words it doesn't stick]

2) Li, abstract, line 1-2 "To determine ... (SESTAMIBI) remains fixed...", and the last three lines ".. clearly undergoes myocardial redistribution.." [with ischemia it washes out sooner]

3) Crane, abstract, line 1-2 "..the mechanism of myocardial retention ..", line 14 "..ischemia results in cellular and mitochondrial calcium "overload" and loss of ..." last 4 lines, "99mTc-sestamibi should not be retained in necrotic or irreversibly ischemic myocardium, ..."

Dr. Fleming

> Subject: RE: soy numbers
> To: rmfmd7@hotmail.com
> From: Mike_Hansen@fd.org
> Date: Wed, 18 Mar 2009 10:44:45 -0500
>
> I have been speaking to Dr. Jay this morning and I think he will be
> brilliant. Do not contact him!
>
> To answer "Why?": That information will not aid the trier of fact
> sufficiently to overcome the risk of any statistical opinion blowing up in
> our face. The jury will only understand "Statistical examination of a set
> of data cannot 'prove' or 'disprove' falsification of data records" and
> they will tune the rest out. This information would only be presented to
> confuse, not clarify anything. A good trial lawyer like the two
> prosecutors in your case could destroy Kaiser without batting an eye. (I
> know I could). This would cause the jury to think that all our experts are
> not credible and you are probably going to get convicted of everything. I
> have no confidence in this evidence to do anything but be a catalyst for
> conviction.
>
> That being said. We need to figure out what our defense is on the soy
> counts. My advice is still for you to finally admit that there were not 60
> participants and stop this charade. Losing this at trial may cost you
> everything, while taking this out of play may provide an opportunity for
> you to continue to practice medicine. The jury will believe Vicki that

> there were around 12 participants involved when she stopped working for
> you. That is nowhere near the 52 that you represented had to have begun
> the study while Vicki was there most of the day. This the jury will
> understand and that's enough. Even if Calkins or Rydberg lost your
> materials. Vicki's testimony along with Tabor getting your excel attachment
> in from 2-25-04 sinks you.
>
> If you really want to help, print out the attached articles and pinpoint
> for me the relevant portions (I know I have missed some) that show that
> the authors believe that the pharmacodynamic properties of sestamibi change
> over time. That mibi does not stick. I want to make sure I haven't missed
> any relevant passages to impeach their experts.
>
> I also want your opinion if we should share the patient images for the
> first 10 counts that you sent to me.
> (See attached file: Maublant.pdf)(See attached file: Li.pdf)(See attached
> file: Eur J Nucl Med Article - Crane.pdf)
> Mike
>
>
>
> RM Fleming
> <rmfmd7@hotmail.c
> om> To
> Mike Hansen PD corrected
> 03/18/2009 10:09 <mike_hansen@fd.org>
> AM cc
>
> Subject
> RE: soy numbers
>
>
>
>
> Mike,
>
> Why?
>
> Dr. Fleming
>
> > Subject: RE: soy numbers
> > To: rmfmd7@hotmail.com
> > From: Mike_Hansen@fd.org
> > Date: Wed, 18 Mar 2009 09:35:30 -0500
> >
> > After reading the report, I stand by my position that we are not

> presenting
> > any statistical evidence in our defense on the last three counts. If you
> > disagree, hire your our lawyer to present whatever statistical evidence
> you
> > want. End of story.
> >
> > Mike
> >

Fukushima

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Fri 3/27/09 2:23 PM

To: RM Fleming (rmfmd7@hotmail.com)

 1 attachment



Ann Nucl ...pdf (205.4 KB)

(See attached file: Ann Nucl Med article.pdf)

Tada!

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 3/27/09 9:46 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)

Mike,

Note these lines out of the abstract. Tada!

"The clearance kinetics of not only MIBI but also
TF is possibly useful for the evaluation of the severity of
ischemia,"

Dr. Fleming

superglue

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 3/30/09 4:57 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

Can you show me a single peer reviewed research paper publication stating "Sestamibi sticks". The only place this is alluded to is the marketing which the company does in it's package insert and website. Marketing is not research. When I spoke with Paknikar this morning, he knew that Khakhakli (sp) - the person at ULCA I sent you emails on who knows Maublant, - knows that if you wait too long for breast imaging you can miss breast cancer (meaning sestamibi washes out).

Dr. Fleming

myoview (tetrafsomin) monograph

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 3/31/09 12:36 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)

 6 attachments



Mike-31 M...doe (41.3 KB), MI size a...pdf (117.9 KB), Resting s...pdf (1175.1 KB), Sestabmib...pdf (1092.7 KB), Sestamibi...pdf (1175.1 KB), Myoview.pdf (251.6 KB)

Mike,

Here is the monograph site for tetrafosmin (aka myoview).

<http://us.myoview.com/essentials/mono/mm05.html>

I am also attaching written notes on the importance of several papers and copies which I have added from references in some of the earlier papers. This should give you even more data.

Dr. Fleming

Ann Nucl Med (2008) 22:617–627
DOI 10.1007/s12149-008-0155-y

ORIGINAL ARTICLE

Monocationic radiotracer kinetics and myocardial infarct size: a perfused rat heart study

David R. Okada · Zhonglin Liu · Delia Beju
Robert D. Okada · Gerald Johnson III

Received: 24 November 2007 / Accepted: 26 April 2008
© The Japanese Society of Nuclear Medicine 2008

Abstract

Objective To compare the myocardial kinetics of three 99m technetium-labeled monocationic tracers [methoxy-isobutylisonitrile (MIBI), tetrofosmin, and Q12] in a model of ischemia–reperfusion (IR) to determine their abilities to assess myocardial viability.

Methods Isolated perfused rat hearts ($n = 30$) were studied in control and IR groups for each tracer. IR hearts were treated with 120 min global no-flow followed by 5 min reflow, then 60 min tracer uptake/clearance. Tracer kinetics were monitored using a scintillation detector.

Results This model produced significant myocardial injury, without significant differences in the percentage of injured myocardium by triphenyltetrazolium chloride (TTC) staining and creatine kinase (CK) assay. Transmission electron microscopy analysis also confirmed necrosis with abundant mitochondrial damage in the IR hearts. All three IR groups exhibited significantly less (mean \pm standard error of the mean) tracer retention than matched controls (MIBI $73.4 \pm 4.9\%$ vs. $96.9 \pm 1.76\%$, tetrofosmin $38.7 \pm 4.6\%$ vs. $82.2 \pm 3.5\%$, and Q12

$23.0 \pm 2.5\%$ vs. $43.8 \pm 1.8\%$, respectively; $P < 0.05$). Tetrofosmin IR hearts exhibited $54 \pm 9\%$ of control myocardial retention, which was significantly less than either MIBI ($86 \pm 5\%$, $P < 0.05$) or Q12 ($63 \pm 6\%$, $P < 0.05$); thus, tetrofosmin provided the best differentiation between nonviable and normal myocardium. Furthermore, tetrofosmin end activity (%id/g) in controls was significantly higher than Q12 (4.09 ± 0.04 vs. 1.71 ± 0.06 , respectively, $P < 0.05$), and tetrofosmin end activity (%id/g) in IR hearts was significantly higher than Q12 (2.19 ± 0.37 vs. 1.06 ± 0.12 , respectively, $P < 0.05$). The correlation between end activity and viable myocardium determined by TTC staining was $r = 0.66$ ($P < 0.05$) for MIBI, $r = 0.94$ ($P < 0.05$) for tetrofosmin, and $r = 0.91$ ($P < 0.05$) for Q12. The correlation between myocardial end activity and myocardial CK leak was $r = -0.62$ ($P < 0.05$) for MIBI, $r = -0.87$ ($P < 0.05$) for tetrofosmin, and $r = -0.89$ ($P < 0.05$) for Q12.

Conclusions Nonviable myocardium can be distinguished from normal myocardium by the retention kinetics of all three monocationic tracers studied. Tetrofosmin and Q12 end activities demonstrate the best correlation with infarct size. However, tetrofosmin kinetics may combine the greatest differentiation between nonviable and normal myocardium, while still retaining adequate activity for imaging.

Keywords 99m Tc · Perfusion imaging agents · Myocardial viability · Ischemia · Reperfusion

Introduction

Noninvasive detection of viable myocardium is clinically important in identifying patients who would

D.R. Okada
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University of Arizona, Tucson, AZ, USA

D. Beju
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myoview (tetrafsomin) monograph

From: **RM Fleming** (rmfind7@hotmail.com)
Sent: Tue 3/31/09 7:36 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)



6 attachments

Mike-31 M...doc (41.3 KB), MI size a...pdf (117.9 KB), Resting s...pdf (1175.1 KB), Sestabmib...pdf (1092.7 KB), Sestamibi...pdf (1175.1 KB), Myoview.pdf (251.6 KB)

Mike,

Here is the monograph site for tetrafosmin (aka myoview).


<http://us.myoview.com/essentials/mono/mm05.html>

I am also attaching written notes on the importance of several papers and copies which I have added from references in some of the earlier papers. This should give you even more data.

Dr. Fleming

sestamibi

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 3/31/09 8:01 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)

Character set:  [Learn more](#)

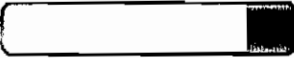
Mike,

Here is the monograph.

<http://us.myoview.com/essentials/mono/mm05.html>

Dr. Fleming


sestamibi

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 3/31/09 8:10 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Character set:  [Learn more](#)
Mike,

<http://www.cardiolite.com/pdfs/cardiolite.pdf>

Dr. Fleming

sestamibi and myoview

From: **RM Fleming** (rmfind7@hotmail.com)
Sent: Tue 3/31/09 8:32 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Character set:  [Learn more](#)

<http://www.oppapers.com/essays/Cardiolite-Vs-Myoview/170329>

RE: sestamibi and myoview

From: **RM Fleming** (rmfmd7@hotmail.com)

Sent: Tue 3/31/09 8:53 PM

To: Mike Hansen PD corrected (mike_hansen@fd.org)

No, I simply sent you what it shows on this. Will be back to you shortly on something else.

> Subject: Re: sestamibi and myoview

> To: rmfmd7@hotmail.com

> From: Mike_Hansen@fd.org

> Date: Tue, 31 Mar 2009 15:39:41 -0500

>

> Did you login and get the whole paper?

>

>

>

> RM Fleming

> <rmfmd7@hotmail.c

> om> To

> Mike Hansen PD corrected

> 03/31/2009 03:31 <mike_hansen@fd.org>

> PM cc

>

> Subject

> sestamibi and myoview

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> <http://www.oppapers.com/essays/Cardiolite-Vs-Myoview/170329>

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sestamibi

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 3/31/09 9:17 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
 1 attachment
cardiolit...pdf (43.6 KB)
Here you go.

sestamibi and washout with cancers

From: **RM Fleming** (rmfind7@hotmail.com)
Sent: Wed 4/01/09 2:15 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

On any given day you can type in something on sestamibi and get published data on washout and it's uses. In this case another example of how it reveals the response of a cancer to chemotherapy.

<http://jco.ascopubs.org/cgi/content/abstract/16/5/1677>

Dr. Fleming

Nuclear Images

From: **RM Fleming** (rmfmd7@hotmail.com)
 Sent: Mon 3/17/08 7:05 PM
 To: Mike Hansen PD corrected (mike_hansen@fd.org)

5 attachments



[Mix & Mat...doc](#) (29.6 KB), [2-color.jpg](#) (391.3 KB), [1-color.jpg](#) (511.2 KB), [2-black a...jpg](#) (512.7 KB), [1-black a...jpg](#) (607.4 KB)

Dear Mike,

I am going to send you several emails today. The first is a document entitled "Mix & Match Sequence". This table, and only this table, shows which 5 minute images go with each 60 minute image from 2002. The top table simply matches the two images along with the patients name. The bottom table shows what I see when I look at the 5 minute image and at the 60 minute image. I cannot guarantee that this matches what I originally read, since these images are not of the quality of my computer monitor and cannot be worked with in any way. This also means that everyone will be seeing the same thing, which for the purposes of what we are doing may be just as well. Any or all of the images may be shown to our expert and depending upon their interpretation, then to whomever else they will need to go to.

I have been confused on how anyone could think that the two images (5 and 60 minutes) show the same thing. I would have thought it was obvious to anyone, they were different. The findings of our recent research demonstrates this beyond any doubt and also establishes the importance of having both images to avoid missing significant disease which could adversely affect patient outcomes. The references sent to you previously and included below also points this out. Two nights ago it dawned on me that if the 5 and 60 minute images show the same thing, then their experts should be able to match the two images together without any difficulty and without any reasonable doubt; hence, the table. I must admit, I would not want to be asked to match up these images. I simply cannot do it without the table. The 5 minute images have the names removed. The 60 minute images still have the names attached. If you think the names should be removed from the 60 minute images, please do so with white out or whatever you prefer. There are 7 patients which I have the color images for and 3 which I do not, as I could not find the old files. For that reason there are 7 sets of color images. However, I have also scanned each image in black and white so instead of asking someone to match 7 sets of color and 3 sets of black and white, they can match 10 sets of black and white and 7 sets of color. I would suggest you do this at depositions so we know how well their experts match the images. If you have them match all 10 black and white and 7 color, you can not only see how well they (interobserver variability) match the 5 and 60 minute images, you can also compare how well they match (interobserver variability) repeatedly. Eg. if on black and white, they match "a" with "8" and on color match "a" with "5" and on repeat efforts with black and white match "a" and "2", well then they not only confirm they cannot match the 5 and 60 minute images (which ought to be a breeze if they so blatantly show the same thing), they also show they are not very reliable. If you need help with the analysis of this, I am sure Dr. Harrington could and would help you.

I will be sending several emails with the attachments due to the volume these images require.

The references are below:

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- ischemia. There is decreased tracer extraction with increasing severity of ischemia. Clearance kinetics (ie washout) may be useful to determine the severity of ischemia.
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 4. VanBrocklin HF, Hanrahan SM, Enas JD, et al. Mitochondrial avid radioprobes. Preparation and evaluation of 7'(Z)-[125I]iodorotenone and 7'(Z)-[125I]iodorotenol. *Nucl Med Biol* 2007;34:109-16. Loss of mitochondrial function is associated with cardiovascular disease.
 5. Tanaka R, Nakamura T, Chiba S, et al. Clinical implication of reverse redistribution on 99mTc-sestamibi images for evaluating ischemic heart disease. *Ann Nucl Med* 2006;20:349-56. Sequential imaging of MIBI useful in detection of ischemia. MIBI washout is frequently observed with ischemia and resulted in a "high" detection of ischemia.
 6. Sugiura T, Takase H, Toriyama T, et al. Usefulness of Tc-99m methoxyisobutylisonitrile scintigraphy for evaluating congestive heart failure. *J Nucl Cardiol* 2006;13:64-8. Evidence increasing that MIBI is not retained in impaired myocardium. MIBI washout rate (WR) useful in evaluating severity of congestive heart failure.
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 11. Takeishi Y, Sukekawa H, Fujiwara S, et al. Reverse redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial infarction. *J Nucl Med* 1996;37:1289-94. Reverse redistribution of 99mTc-sestamibi has been noted in patients with coronary artery disease. MIBI redistribution after PTCA validates patent infarct-related artery and preserved left ventricular function.

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"Some investigators have found relatively poor relationships between lung uptake and coronary stenoses when measured on MIBI tomographic acquisitions at 1 hr after stress injection" "Measurements obtained early poststress in our study, but not those obtained under other physiologic conditions, were strongly correlated with the extent and severity of coronary disease." "Our results suggest a similar interpretation of lung uptake for MIBI whether stress is performed with vasodilators or with exercise alone. "In our laboratory, the particular stress modality used did not significantly affect the frequency of increased lung uptake, but this findings requires verification by centers where stress is performed with other protocols." (We can now verify this.) "In the minutes after injection, MIBI undergoes more dynamic change than is the case with 201 Tl". "Increased lung uptake on immediate (4-min) poststress images with MIBI is seen in a significant portion of studies with abnormalities on perfusion tomograms. This potential ancillary diagnostic sing appears related to ischemic perfusion defects, may be induced with exercise alone or with dipyridamole-based stress, and it is seen more frequently with severe disease." ... "By comparison, lung uptake on delayed (1-hr) MIBI images is less frequent, and it appears related to fixed defects and to poor ventricular function. Further investigation of the potential value of early poststress MIBI images may result in the recovery of an important ancillary diagnostic sign, which appears to have been lost with the transition from 201Tl- to 99mTc-based perfusion agents." I.e. increased lung uptake (increased L:H or decreased H:L) at 4 mintues is associated with greater ischemia. The research was first completed in 1996.

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- Dobutamine. MPI detects blood flow disparities between regions supplied by "Normal" and "stenotic" arteries.
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 37. Fleming RM., Boyd L., Forster M. Angina is Caused by Regional Blood Flow Differences - Proof of a Physiologic (Not Anatomic) Narrowing, Joint Session of the European Society of Cardiology and the American College of Cardiology, Annual American College of Cardiology Scientific Sessions, Anaheim, California, USA, 12 March 2000, 49th (Placed on internet www.prouson.com for physician training and CME credit, April 2000.) Angina is the result of regional blood flow differences which can be determined by quantifying regions of interest (ROIs). This can be quantified using MPI (myocardial perfusion imaging.).
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46. Fleming RM.: Chapter 31. *Nuclear Cardiology: Its Role in the Detection and Management of Coronary Artery Disease* *Textbook of Angiology*. John C. Chang Editor, Springer-Verlag New York, NY 1999, pp. 397-406. **Chapter which I wrote showing not one, but multiple approaches for doing rest/stress imaging. This was the state of the art in 1995 which chapter written. THINGS HAVE EVOLVED!**

Yours,

Dr. Fleming

FW: matching images

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 3/18/08 6:02 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)

Dear Mike,

- > It seems simple to me regarding the images I sent yesterday.
- > In deposition, ask Federal's experts to match images.
- > If matching is done, record accuracy. If witness testifies he/she cannot match
- > get clear testimony that images at 5 and 60 minutes differ.
- >

Yours,

Dr. Fleming

an idea

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 8/27/08 1:25 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

In addition to all the work we are doing here, the lectures I am giving, the number of people we are running this study on (both here and elsewhere in the country), it dawned on me this morning that in addition to having their experts try to match 10 black and white static (5 minute) and dynamic (60 minute) images, we should give their experts the first static and first dynamic images (which are from different patients) and ask them to explain why they represent the same thing. After they have finished with their explanation, you can point out how interesting it is that the 5 and 60 minute images are identical since they come from different patients.

Yours,

Dr. Fleming

5 and 60 minute images

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 12/16/08 5:10 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Dear Mike,

If I were the person to ask questions of any Nuclear Cardiologist, be they ours or the other side, I would ask the following questions (which I think will help any Nuclear Cardiologist you find, to decide we are right):

1. Have you ever looked at 5 and 60 minute images of the heart post-stress?
2. Have you read the references quoted on the ASNC website which shows that Sestamibi washes out in 28 minutes and is less time if ischemia (that would be what we are looking for) is present? Are they familiar with these peer review published manuscripts?
3. If they believe that the 5 and 60 minute images are identical, then they need to match up the 5 and 60 minute images from the 10 cases without knowing which 5 minute image is associated with which 60 minute image. In other words, if there is no difference between 5 and 60 minute results, then there should be no problem matching them and I gave you a key (table) already.
4. How many images are there? Is there only 1 or more than 1 for each study.
5. What other questions would you consider pertinent Mike?

Yours,

Dr. Fleming

20 images

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Thu 3/26/09 8:22 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

There were 20 images (10 at 5 minutes and 10 at 60 minutes) which you have as 10 labelled by letters and 10 labelled as numbers.

Dr. Fleming

FW: 0671

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Thu 4/16/09 8:08 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)

 6 attachments

data.jpg (532.4 KB), EKG.jpg (1765.6 KB), final rep...jpg (1816.7 KB), scan0004.jpg (579.9 KB),
scan0005.jpg (591.0 KB), scan0006.jpg (1402.2 KB)

What the questions were for Wallenmeyer

From: kayla6151@hotmail.com
To: rmfmd7@hotmail.com
Subject: 0671
Date: Mon, 29 Sep 2008 01:37:17 +0000

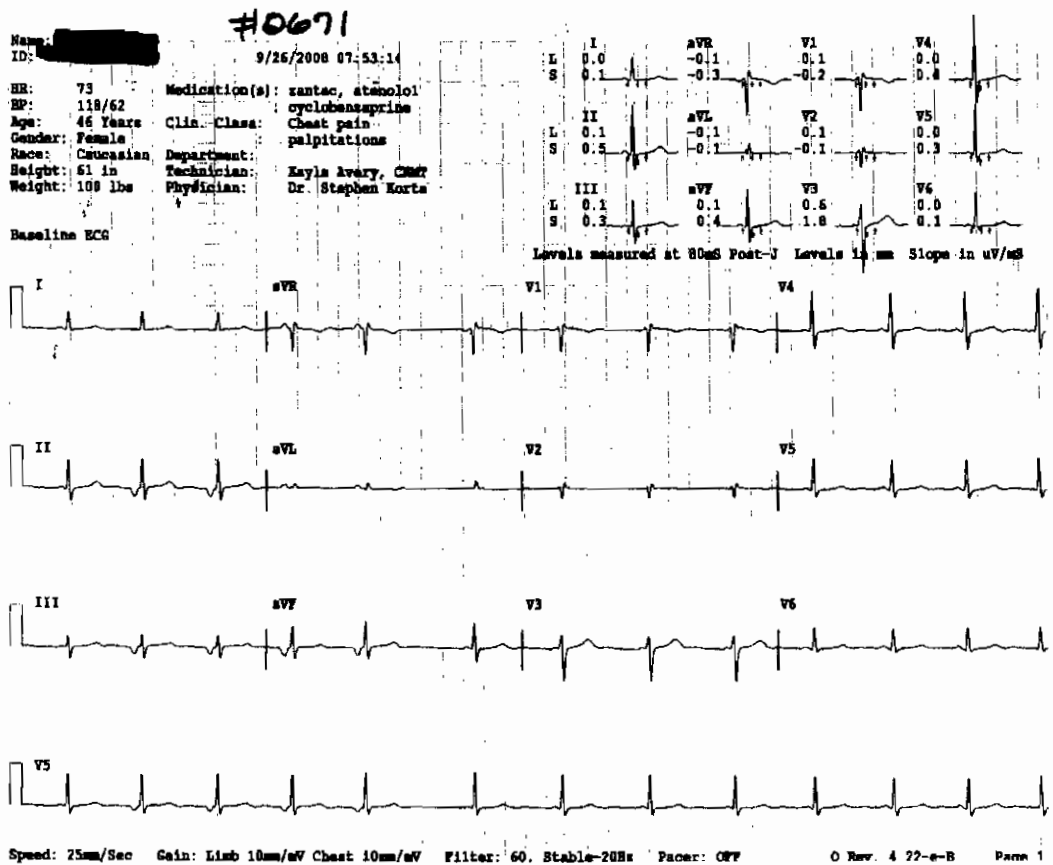
0671

Regions of Interest Data Collection
 Sequential Myocardial Perfusion Imaging
 Cardiovascular Institute of Southern Missouri

Patient Identifier: 0671

Date of Study: 9/24/08

	5 Minute Static Rest	60 Minute Static Rest	60 Minute Dynamic Rest		5 Minute Static Stress	60 Minute Static Stress	60 Minute Dynamic Stress
Basal Anterior	4728	7013	1385		26171	16281	4282
Mid Anterior	8730	8542	1347		10976	30200	7184
Basal Anterolateral	10074	6526	2908		12504	14453	4754
Mid Anterolateral	10531	6916	2640		20084	23024	8078
Basal Inferior/Posterior	6268	4700	983		22249	23394	7461
Mid Inferior	13783	7167	1103		37852	14298	3483
Basal Inferoseptal	11150	4959	2401		24051	26496	5821
Mid Inferoseptal	7918	5544	2225		25040	24285	6072
Total Heart	208760	118823	41779		542396	367396	123114
Total Lung	91747	54383			287030	204645	



#671

Name: [REDACTED] ID: [REDACTED] 9/26/2008 08:58:06 FINAL REPORT TEST SUMMARY

Medication(s): santon, atenolol
 Age: 46 Years Cln. Class: cyclobenzaprine
 Gender: Female Race: Caucasian Department: Chest pain
 Height: 61 in Technician: Kayla Kvery, CMPT palpitations
 Weight: 100 lbs Physician: Dr. Stephen Korte

Protocol: Bruce (00:24), Manual (09:09)

TIME	PHASE	MPH	GRADE	HR	BP	RPP	MEETS	ECG/EC	HPE	EVENTS
00:00	Exercise	0.0	0.0	68			1.0			
00:24	Exercise	1.2	0.0	89			1.1			
01:00	Exercise	1.2	9.0	87	118/62	102	1.4			
02:00	Exercise	1.7	10.1	93	120/62	111	2.0			
03:00	Exercise	2.2	10.1	102	120/62	122	4.2			
04:00	Exercise	2.5	12.1	105			5.4			
05:00	Exercise	2.5	11.9	112	124/70	138	6.6			
06:00	Exercise	3.0	12.5	130	125/70	162	7.2			
07:00	Exercise	3.5	14.1	141			8.5			
07:56	Exercise	3.5	14.1	151	130/78	196	9.5			
08:08	Exercise	3.5	14.1	149	130/78	199	9.6			
09:00	Exercise	3.5	14.1	156	130/78	202	10.4			
09:33	Max Exer.	3.5	14.1	160			10.4			
01:00	Recovery	0.0	0.0	142	130/74	184	5.5			
02:00	Recovery	0.0	0.0	122	148/80	100	1.9			
03:00	Recovery	0.0	0.0	112			1.0			
03:26	Recovery	0.0	0.0	104	120/64	124	1.0			
04:00	Recovery	0.0	0.0	96	120/64	115	1.0			
05:00	Recovery	0.0	0.0	96			1.0			
06:00	Recovery	0.0	0.0	95	120/60	114	1.0			
07:00	Recovery	0.0	0.0	89			1.0			
08:00	Recovery	0.0	0.0	90	120/60	100	1.0			
09:00	Recovery	0.0	0.0	90			1.0			

Summary:

- The Exercise test ran for 09:33 mins. Peak MEETS was 10.5.
- A peak heart rate of 161 bpm was achieved at 09:12 mins in exercise.
- 93% of the 174 bpm max was reached.
- The peak BP was 148/80 (during Recovery). Baseline was 118/62.

ST SEGMENT ANALYSIS:

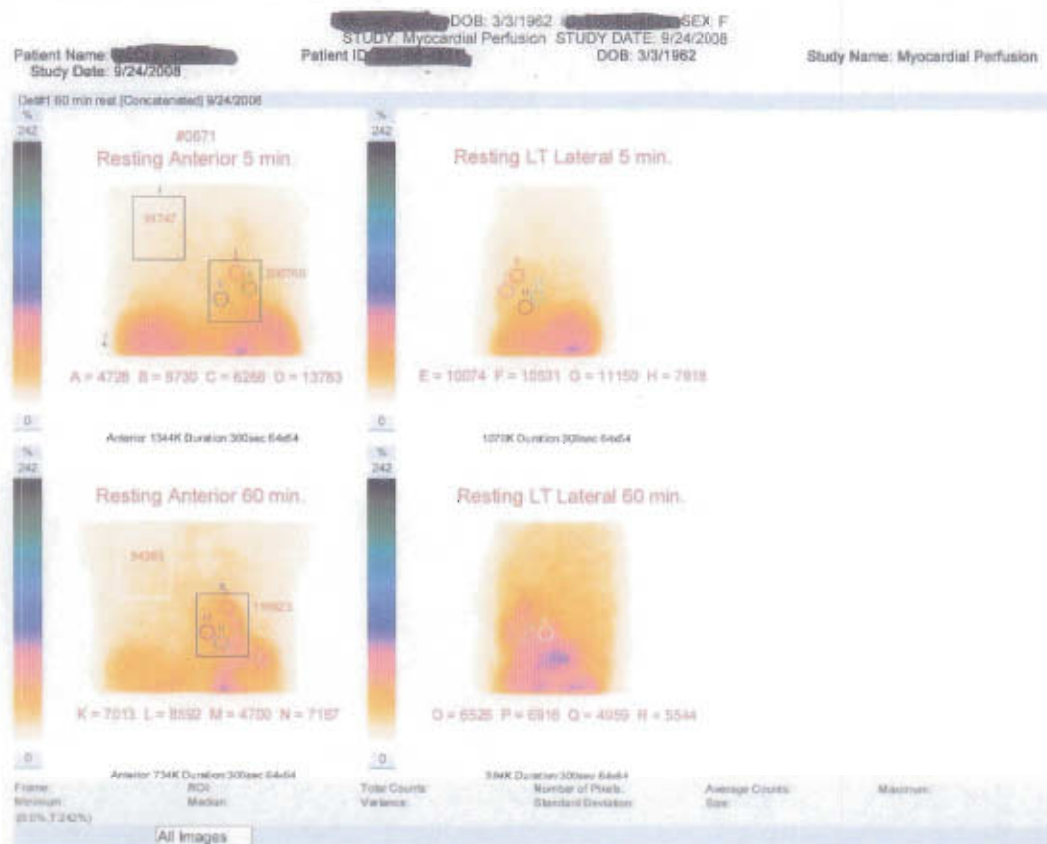
- Lead II first exhibited ST depression exceeding 1mm at 09:00 of Exercise.
- ST depression exceeded 1mm for 00:10 mins.
- 1.2mm maximum depression in II was exhibited at 09:00 mins of Exercise.
- At 00:07 of Recovery ST segment returned to baseline.

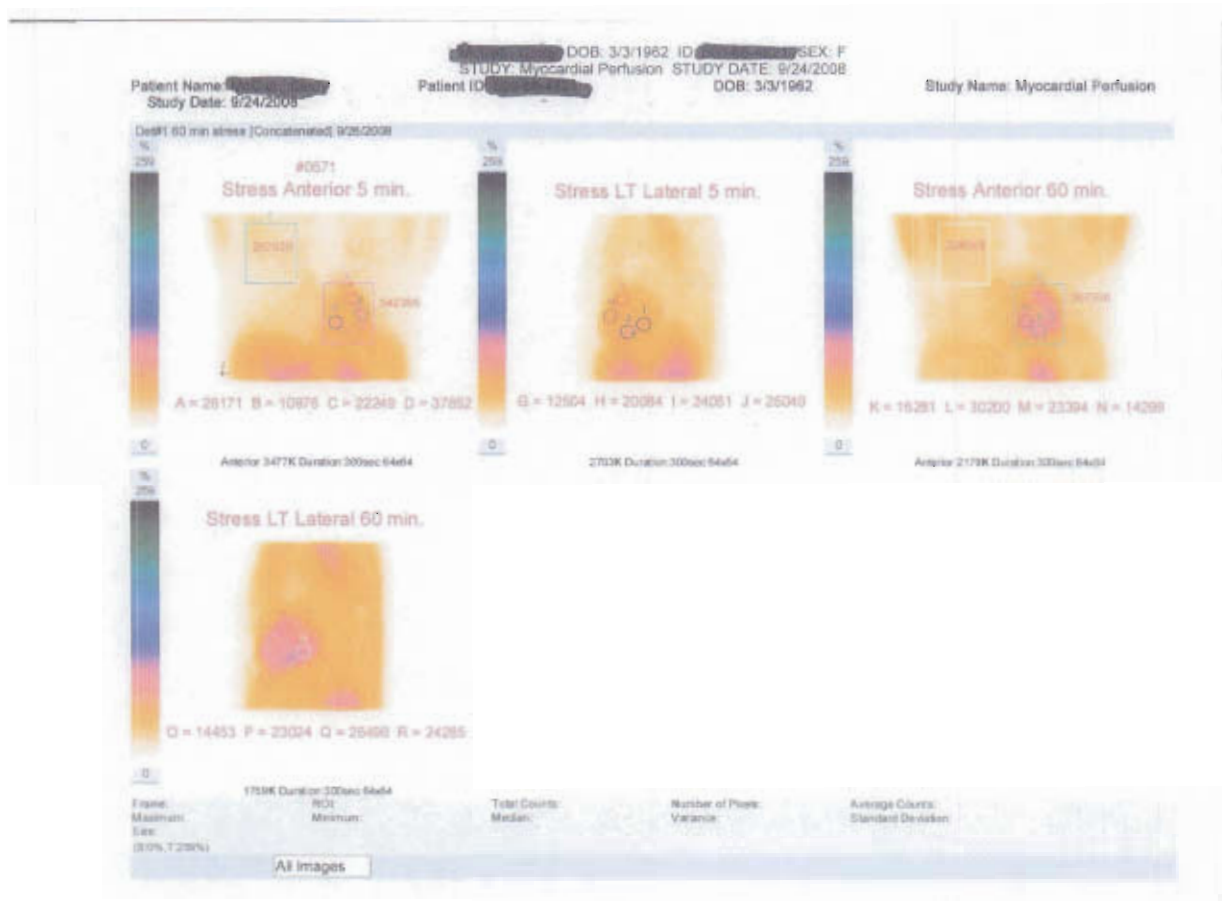
COMMENTS:

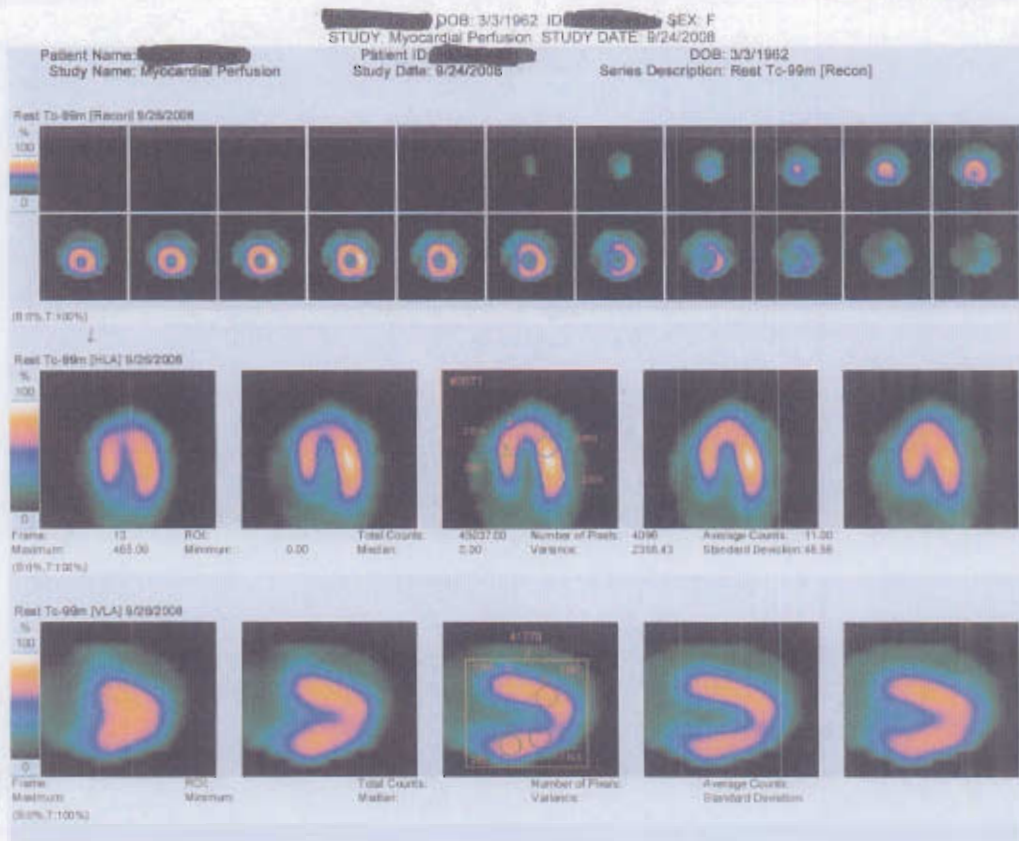
TMET stress nuclear SPWCT with Cardiolite to 9:5 min 14% grade, 3.4 MPH with fatigue, no chest pain/arrhythmia. No sig ECG changes, see nuclear report. S. Korte MD

32 mCi Cardiolite

Manual protocol SPWCT follows







CURRICULUM VITAE

NAME: Richard M. Fleming, M.D.
F.A.S.N.C. (Diplomate), F.A.C.P., F.A.S.A.
Preventive & Nuclear Cardiologist, Internist,
Researcher & Author

CURRENT POSITION: Cardiologist, Reno, NV &
Cardiovascular Institute of Southern Missouri
Poplar Bluff, MO

PRESENT TITLES: Nuclear & Preventive Cardiologist
Reno, NV

BIRTH DATE: 02/17/56

CHILDREN: Stephanie Erin Fleming
Christian Michael Fleming
Matthew Ryan Fleming

CITIZENSHIP: USA.

EDUCATIONAL EXPERIENCE

UNDERGRADUATE EDUCATION:

University of Iowa, Iowa City, Iowa, Undergraduate Studies, Jan. - May 1976.

Hawkeye Institute of Technology, Waterloo, Iowa, Emergency Medical
Technician – Ambulance (07-29-07), 1977 - 1978.

University of Northern Iowa, Cedar Falls, Iowa, BA. General Science, Biology,
Psychology; Minor in Chemistry, Graduated *Cum Laude*, 1980.

GRADUATE EDUCATION:

University of Northern Iowa, Cedar Falls, Iowa, Graduate Studies in Psychology, 1980 - 1981. Prof. Gordon Harrington (Mentor)

University of Iowa Medical School, Iowa City, Iowa, Medical Doctorate, *Graduated with Honors Program - Internal Medicine*, 1986.

POSTGRADUATE TRAINING:

Internship, University of Iowa Program B, 1986-1987

Internal Medicine Residency, Creighton University, Omaha, Nebraska, 1987 - 1989.

Cardiology Fellowship, University of Texas at Houston, Houston, Texas 1989 - 1992. Dr. K. Lance Gould (Mentor-PET)

Institute for Nuclear Medical Education, Boulder, Colorado, 1991.

Principles of Radiation Physics
Medical Radiation Instrumentation
Medical Radiation Protection
Radiopharmaceuticals and Chemistry.

Cardiolite Clinical Training Program (Nuclear Cardiology) - 1991

Positron Emission Tomography (PET) Certification 1991 - 1992

TEACHING POSITIONS

UNDERGRADUATE

Instructor, (Classes through Department of Physical Education), Cardiopulmonary Resuscitation and First Aid, University of Northern Iowa, Cedar Falls, Iowa 1976 - 1979.

Laboratory Instructor, Department of Biology, University of Northern Iowa, Cedar Falls, Iowa 1977 - 1980.

GRADUATE

Graduate Teaching Assistant, Department of Psychology, University of Northern Iowa, Cedar Falls, Iowa 1980 - 1981.

MEDICAL SCHOOL

Phlebotomist and Trainer, University of Iowa Hospitals and Clinics, Iowa City, Iowa 1982-1983.

CPR – Basic (Affiliate Faculty) and ACLS (I/T) Assistant for classes at University of Iowa, Iowa City, Iowa, 1982-1984.

CARDIOLOGY

Clinical Instructor/Cardiology Fellow, Department of Cardiology, University of Texas Health Science Center at Houston, Houston, Texas, 1989-1992.

Director of Nuclear Cardiology and Lipid Research, the Center for Clinical Cardiology & Research, Iowa, 1992–1995.

Development Effort of a Nuclear Technologist Program for Methodist College, Omaha, NE, with Pat Sullivan, July 1998-April 1999.

Clinical Service Association, Department of Cardiology, Creighton University, Omaha, NE, 1999-2004.

The Fleming Heart & Health Institute, Omaha, NE, 1999-2004

Veterans Administration Health Care System, February 2005 – Present.

Gulf Coast Veterans Health Care System, Biloxi, MS, 2005-2007

VA Central Iowa Health Care System, Des Moines, IA, 2005-2008

VA Sierra Nevada Health Care System, Reno, NV, 2005-2007

Exercise Stress Testing Certification Director for IM Residents, 2005-2007

Electrocardiogram Conference Director for IM Residents, Morning Report, 2006-2007

Nuclear Cardiology Reviewer, January 2006-2007

Physician Services Contractor – Inspecting Military Medical Facilities, 2007

Cardiologist, Cardiovascular Institute of Southern Missouri, Poplar Bluff, MO, 2008-Present

RADIATION ONCOLOGY

Adjunct Assistant Professor, Radiation Oncology Department, University of Nebraska Medical Center, Dr. Charles Enke, September 1, 2000 – December 5, 2005.

PHYSICS

Adjunct Professor, Department of Physics, Hampton University, Hampton, VA
Proposed 2005, Studies in Development with FH Washout.

HOSPITAL, CLINIC, CONSULTATIVE or INSTITUTE APPOINTMENTS

STAT Care Physicians, Houston, Texas 1990-1992
San Jacinto Methodist, Baytown, TX 1991-1992
Twelve Oaks Hospital, Houston, TX 1990-1992
Gulf Coast Hospital (now closed), Houston, TX 1990-1992
Westbury Hospital, (now Cornerstone Hospital of Houston), Houston, TX 1990-1992
Center for Clinical Cardiology and Research, 1992-1995
Delaware County Memorial Hospital, Manchester, Iowa, 1992-1993
Virginia Gay Hospital, Vinton, Iowa 1992-1993
Acute Care, Inc., Ankeny, Iowa 1993-2002
Sartori Memorial Hospital, Cedar Falls, Iowa 1993-1994
Pella Community Hospital, Pella, Iowa 1994-1994
Buena Vista Regional Medical Center, Storm Lake, Iowa 1994-1996
Marshalltown Medical and Surgical Center, Marshalltown, Iowa 1994-1994
Consultants in Cardiology (clinic facility known as Midlands Medical Clinic), Dr. Vincent Miscia, Omaha, Nebraska, 1994-1995
Floyd Valley Hospital, LeMars, Iowa, 1995-1996
Our Lady of Lourdes Hospital (now Faith Regional), Norfolk, Nebraska 1995-1996
Heartland Medical Clinic, Omaha, Nebraska, 1995 - 1996
Saint Joseph's Hospital, Omaha, Nebraska, 1987 - 1989
Medical Director & President, Integrated Physicians of Nebraska, PC, 1996-1999
Columbus Community Hospital, Columbus, NE. Consulting Physician, 1998 - 2002.
MDS Harris Consultant, Lincoln & Omaha, NE 1998-1999
Shenandoah Memorial Hospital, Shenandoah, IA, 1998-2001
Missouri Valley Hospital (now Alegent Health Community Memorial Hospital), Missouri Valley, IA, 2000-2001
The Fleming Heart & Health Institute, Omaha, NE, 1999 - 2004
Creighton University Medical Center, Omaha, NE, 1999-2004.
The Camelot Foundation (Not-for-Profit), 2000-2005
University of Nebraska Medical Center, Adjunct Professor, Department of Radiation Oncology, Omaha, NE, 2000-2005.
Hampton University, Center for Advanced Instrumentation, Adjunct Professor, Department of Physics, Hampton, VA, Proposed 2005
Veterans Administration Hospital, Biloxi, Mississippi. 2005-2007.
Veterans Administration Hospital, Des Moines, Iowa. 2005-2008.

Veterans Administration Hospital, Reno, Nevada, 2005-2007
Inspector for Military Medical Facilities, 2007
Poplar Bluff Regional Medical Center, 2008 - Present

LICENSURES

Iowa License # 26135, July 1, 1987 (Active)
Nebraska License # 17502, August 10, 1987- Oct 1, 2004 (Inactive)
Texas License #H7414, June 12, 1990 - Feb 28, 2004. (Inactive)
Illinois License #036-108577, February 11, 2003 – July 31, 2005 (Inactive)
Oklahoma License #24141, July 23, 2004 – July 1, 2005 (Inactive)
Missouri License #2005031306, September 26, 2005 (Active)
Radioactive Material License L04513 Texas, 1991
Radioactive Material License 0232-1-57-M2 Iowa, 1992
Radioactive Material License 01-91-01 Nebraska, 1999-2004.

CERTIFICATION EXAMINATIONS

Flexnor Examination, Iowa State Board of Medical Examiners Components I & II, June 1986.

American Board of Internal Medicine September 12, 1990 (#126107)
Re-certification started 2005

Hazard Communication Training, UTHSCH, Jan. 1990

Nuclear Medical Education 1991
Medical Radiation Protection (Completion & Competency)
Radiopharmaceuticals and Chemistry (Completion & Competency)
Principles of Radiation Physics (Completion & Competency)
Medical Radiation Instrumentation (Completion & Competency)

Technetium generator eluting, quality control and disposal, 1991

Fundamentals of PET and Computer Applications, March 1992

Interpretation of Percent Diameter Stenosis from Coronary Arteriograms, (# 001)
April 1994

Board Certified/Diplomate in Nuclear Cardiology, October 22, 1996 (#125)
The Certification Council of Nuclear Cardiology (CCNC).
www.cbnc.org/status.cfm

PROFESSIONAL ORGANIZATIONS

Premedical

Beta Beta Beta Biological Honor Society, Delta Iota, 1978.

Officer of Tri-Beta Biology Honor Society, University of Northern Iowa, 1978 - 1981.

Medical School

Caduceus Medical Education, University of Iowa College of Medicine,

Vice - President 1981

President 1982.

Scientific Societies

Physicians for Social Responsibility, 1982 - 1987.

American Association for the Advancement of Science, Member, 1992 - 1998

New York Academy of Sciences. Full Member 1994 - 1996

American Medical Student Association 1981 - 1998.

American Medical Association, 1986 - 1998, 2006 - Present. 01803861800

Member of the American Board of Radiation Safety (ABMRSO) Officers, 1992 - 1998.

Fellow of the American College of Angiology, 1990.

American Association for Nuclear Cardiology Full Member, 1992 - 1996.

Founding Fellow American Society of Nuclear Cardiology, 1996.

Fellow International College of Angiology, 1994.

Fellow American College of Physicians/American Society of Internal Medicine, 2000.

Fellow American Society of Angiology, 2006.

Specific Invited Medical Colleges

American College of Physicians 1986

Associate 1986 - 1991

Member 1991 - 2000 (00025926)

Fellow 2001 – Present.

Fellow American College of Angiology 1992

Fellow International College of Angiology 1994

Diplomate - American Society of Nuclear Cardiology 1996

International Society for Heart Research 1996

Fellow of the American College of Physicians-American Society of Internal Medicine, 2000 – Present.

Fellow of the American Society of Angiology, 2006

Medical Societies

American Medical Association 1986 - 1999

Texas State Medical Society 1990 - 1992

Harris County Medical Society (Texas) 1990 - 1992

American College of Angiology 1992

Iowa State Medical Society 1993 - 1995

International College of Angiology 1994

American Society of Nuclear Cardiology 1996.

International Society for Heart Research 1996

Non-Medical Organizations

Promise Keepers 1994

The Omaha Club 1996 - 2000

The Greater Omaha Chamber of Commerce 1999

Committee Chair Pack 60 Cub Scouts 2001 - 2003

Committee Chair Troop 461 Boy Scouts 2002 – 2003

Board of Trustees, Mid-America Council, BSA, 2003 – 2004

Knights of Columbus, 4th degree, 2003.

American Heart Association

American Heart Association - Iowa Heart Affiliate, 1976 - 1989.

Basic Life Support Instructor, 1976 - 1981.

Basic Life Support Instructor - Trainer, 1981 - 1986, and 1992 - 1994

Advanced Cardiac Life Support Instructor, 1986 - 1988, 2006 - Present.

President of the Pottowattamie Unit, Iowa Heart Association, 1988 - 1989.

Physician Cholesterol Education Faculty - Iowa Heart Association, 1988 - 1989.

American Heart Association - Nebraska Affiliate 1995 - 1996

American Heart Association, Member on **the National Council on Circulation**, 1990 - Present.

Nominated for **National Council - Nutrition Committee**, American Heart Association. September 2001.

Advanced Cardiac Life Support, *Experienced Provider*, November 2006 - Present.

Advanced Cardiac Life Support, *Experienced Provider Faculty*. 2007-Present

COMMITTEES

Policy Committee for the Iowa Heart Association, Standards for Performing and Certifying in BCLS, 1988 - 1989

Call for Help Committee, Iowa Heart Association, 1988 - 1989

Member for Proposed Board of American Association for Nuclear Cardiology (AANC), 1992 - 1997

Member of the American Board of Medical Radiation Safety Officers (ABMRSO). 1992 - 1997

American Heart Association - Nebraska Affiliate
Program Committee for Douglas County, 1995 - 1997
Program Committee for Sarpy County, 1995 - 1997

Board Member of Nebraska Heart Association
Douglas County March 1995 - 1997
Sarpy County March 1995 - 1997

Training and Credentialing Committee - American Society of Nuclear Cardiology
CCNC Examination Committee 1997 - 2002
CCNC Sub-Chairman 1997 - 2002

Member of Advisory Board, University of Northern Iowa, College of Natural Sciences Industrial Advisory Board, 1997 - 2005.

Our Healthy Community Partnership - Health Advisory Board 1997 - 1999.

Roundtable member for National Meeting "Build a Better Bridge: Improving working relations, communications, and referrals between traditional and alternative health care." American Chiropractic Association Headquarters, Arlington, VA, March 23, 1998.

Advisor for the TriCor (fenofibrate) Advisory Meeting - April 17, 1998, Chicago, IL (Abbott)

Board Member of the National Training and Credentialing Committee American Society of Nuclear Cardiology (with ACC and AHA) 1999 - 2002.

International College of Angiology **Board Member**, July 2000 - 2001.

Co-Chairman of Membership Committee for the International College of Angiology, July 2000 - 2001.

Consultant to Advisory Meeting: "Increasing Cardiac Oxygen Efficiency: The Missing Piece in the Management of Chronic Ischemic Heart Disease." New Orleans, LA, November 11, 2000.

Nominated to **Editorial Board** Preventive Cardiology, October 2001.

Advisory Board Member for The American Breast Cancer Guide, February 2002.

Lipid consultant board. Abbott pharmaceutical company. May 10-11, 2002.

Reviewer for Lipid abstracts for American Heart Association, 2001 – Present.

ICU Education Committee, Sierra Nevada Health Care System. 2006 - 2007.

PBRMC (Poplar Bluff Regional Medical Community) D2B (Door-to-Balloon) Cath Lab Activation Protocol Committee. 2008.

HONORS, AWARDS AND RECOGNITIONS

Iowa High School Science Student, *Physics* Competition, 1973 - 1974.

American Association of Retired Persons, Medical Scholarship, 1985 - 1986.

Senior Honors in Internal Medicine, University of Iowa, 1985- 1986.

Allen Memorial Foundation Service Award, Allen Memorial Hospital, Waterloo, Iowa 1989.

American Heart Association, *Iowa Affiliate Faculty Award*, 1989.

Who's Who Among Rising Young Americans, 1991

Nomination and Approval for Fellowship, American College of Angiology. 1992

Recommended to Governor of Iowa as Future Member of the Iowa State Board of Health. 1994 and 2000.

Nomination and Approval for Fellowship, International College of Angiology. 1994.

Nominated for the Young Investigator Award. Presentation 41st Annual World Assembly, American College of Angiology. San Antonio, Texas October 1994.

Invited to present on lipid management at the 5th World Congress on Heart Failure, Washington, DC, May 1997

Strathmore's Who's Who - July 1997, Lifetime Member

Advisory Panel to Graduate Dean of Sciences, University of Northern Iowa, July 1997.

Nominated for the John B. Chang International College of Angiology Award, 1998.

Co-Chair *Atherosclerosis Session*, 40th Annual World Congress, the International College of Angiology Meetings, Lisbon, Portugal, 28 June - 3 July, 1998

National Advisory Board for America Talks Health Network - Expert in Field of Cardiology. April 1998.

KRTK FM 97.1 Nationally Syndicated Radio Talk Program America Talks Health", "Award for 1998 Breakthroughs in Heart Disease" Dr. Keith Robinson, Houston, TX 23 January 1999.

Co-Chair *Coronary Artery Disease* - I Session, 41st Annual World Congress, the International College of Angiology Meetings, Sapporo, Japan 7 July 1999

Co-Chair *Basic Research* - I Session, 41st Annual World Congress, the International College of Angiology Meetings, Sapporo, Japan 7 July 1999

Chairman *Atherosclerosis Session*, 41st Annual World Congress, the International College of Angiology Meetings, Sapporo, Japan 7 July 1999

Co-Chair Prognostic Implications of Risk Factor Modification, American College of Cardiology meetings, Anaheim, CA, March 2000.

Honorary Lecturer at the American College for Advancement in Medicine, the Denham Harman Lecture, Inflammation and Coronary Artery Disease (The Fleming Unified Theory of Vascular Disease), Dallas, TX, May 5, 2000.

Invited presenter for the USDA Research Program on Health and Nutrition Effects of Popular Weight-Loss Diets Public Meeting. Request for Deputy Secretary Dr. Kennedy to present both **Oral and Written Testimony** entitled "*Obesity and Related Health Problems are the Result of Too Many Calories and Too Much Saturated Fat Regardless of the Misconceptions Promoted by Many Popular Weight Loss Programs*". January 11, 2001. USDA South Agriculture Building, Jefferson Auditorium, Washington, DC.

Abstract Evaluator for University of Nebraska Medical School 5th Annual Cardiovascular Disease Symposium, Omaha, NE February 9, 2001.

Keynote speaker at the 5th Annual International Congress of BioEnergetic Medicine. Orlando, Fl., May 26, 2001.

Abstract grader for "Lipid Disorders and Lipoprotein Metabolism" to be presented at the American Heart Association Scientific Sessions. June 2001.

Member of the Selection Team for "Lipid Disorders and Lipoprotein Metabolism" for the November 2001 Scientific Sessions of the American Heart Association. July 2001.

Co-Chair and Moderator for "Cholesterol-Rich Lipoprotein Metabolism" session, 2001 Annual Scientific Sessions of the American Heart Association. Anaheim, CA, USA, 14 November 2001.

Reviewer for the Asia - Pacific Forum "The Genomics Revolution: Bench to Bedside to Community" and the 42nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention." Honolulu, Hawaii, USA, 23-26 April 2002.

Member of the Selection Team for "Lipid Disorders and Lipoprotein Metabolism" for the Scientific Sessions of the American Heart Association. 2002, 2003 and 2004.

Invited Guest of the American Dietetic Association, 85th ADA Annual meeting, Philadelphia, PA 19-22 October 2002.

Physician of the Year Award 2003, Washington, DC, February 25, 2003.

Co-Chair for Health and Nutrition Session, American Oil Chemists Society, Kansas City, MO, May 7, 2003.

Member of ABC news expert group on Diet and Nutrition. 2004 – Present.

Member of ABC news expert group on Cardiovascular Disease 2005 – Present.

Second place/runner-up poster presentation, "What effect do isocaloric low-fat, low-carbohydrate and moderate-fat diets have on obesity and inflammatory coronary artery disease?" 8th International Conference, Vascular Endothelium: Translating Discoveries into Public Health Practice. Sponsored by the CDC, Crete, Greece, 29 June 2005.

Invited member of Speakers Bureau for Society of Nuclear Medicine (Molecular Imaging) 19 March 2008.

SERVICE TO COMMUNITY (Including talks, radio, TV and newspaper):

Training/Lectures:

CPR Instructor Participation in the Allen Hospital Cardiac Rehabilitation Program, Waterloo, Iowa, 1976 - 1977.

Emergency Medical Technician and Member of the University of Northern Iowa Rescue Squad, Cedar Falls, Iowa, 1976 - 1980.

Basic Cardiopulmonary Resuscitation Classes, American Heart Association, Iowa Affiliate, 1976 - 1989.

Faculty Lecturer for the Physicians Cholesterol Education Program, 1988 - 1989.

Hypercholesterolemia and Its Treatment, University of Texas at Houston, Internal Medicine Residents, October 18, 1990.

Hypercholesterolemia and Coronary Heart Disease, Second Annual Family Practice Medicine for the 90's, October 25, 1990.

Reversal Therapy and Coronary Heart Disease, Second Annual Family Practice Medicine for the 90's, October 25, 1990.

An Update on Nuclear Cardiology, Cedar Rapids and Community Physicians, Cedar Rapids, Iowa November 30, 1992.

Faculty for the Fifth Annual Cedar Rapids Heart Symposium for the Practicing Primary Care Physician. Medical Case Studies. February 26, 1993.

Modifying Your Risk Factors After Your Heart Attack or Coronary Artery Bypass Operation. Iz Lewis Zipper Club, Omaha, Nebraska, February 22, 1995.

Heart at Work Program presented at Midlands Community Hospital, April 12, 1995

Co-Chairman for the Smith Barney American Heart Walk, Nebraska Heart Association, AHA, 1995 and 1996.

West Omaha Rotary Club, Omaha, NE, "Heart Disease" Talk, August 22, 1997.

River City Reagents, Omaha Club, Omaha, NE, September 5, 1997.

Free Public Seminar "How Changing Your Diet Could Help You Live Longer", Embassy Suites Hotel, Omaha, NE, September 28, 1997.

River Oaks Country Club Lecture Series, Coronary Artery Disease and How to Bypass Your Bypass. Houston, TX. October 3, 1997.

Unique Books of River Oaks, Houston, TX, Talk (Hosted by Dr. Denton and Mrs. Cooley), October 3, 1997. Invited guests included: President and Mrs. Bush, Mr. David Brinkley.

The University of Northern Iowa, Cedar Falls, IA, "Nuclear Cardiology and Heart Disease." Lantz Auditorium, October 11, 1997.

The Writers Harvest, National Benefit to aid with Hunger and Poverty, Sponsored by Barnes & Nobles Nationally, Omaha, NE, October 23, 1997.

Our Healthy Community Partnership - Public Health Policies for Douglas and Sarpy County, Nebraska. November 1997.

The Alternative Healing Expo at the Phoenix Center & Unity Church of Omaha, "How to Bypass Your Bypass". The Truths and Falacies of Diet, Nutrition and Disease. January 24, 1998.

Womens Health Fair at Aksarben, Cholesterol Screening and Discussion of Womens Risk for Heart Disease, Omaha, NE, February 21, 1998.

National Advisory Board for America Talks Health Network - Expert in Field of Cardiology, Houston, TX, April 1998.

Houston Rotary Club, Galleria, Talk "Heart Disease, What Causes It and What You Can Do About It.", Houston, TX, April 13, 1998. Invited Guests include Judge McSpadden.

Houston Forum Speakers Bureau, "The Pathogenesis of Vascular Disease, Where Are We Headed?" Houston, TX, April 16, 1998.

Hickory Hills Elementary School, Papillion, NE, Talk with second and fourth grade students about Heart Disease and Writing, 17 September 1998.

Papillion - LaVista Public Schools Community Connection, "Students Learn About the Heart." Papillion - LaVista, NE, October 1998.

District 66 Schools, "Smoking Cessation Program/Class" for High-School Students, Omaha, NE, January-May (Spring Semester) 1999.

"How Does Your Heart Work", A presentation to third graders at Hickory Hills Elementary School, February 9, 2000.

The Human Heart, A presentation to fifth graders at Hickory Hills Elementary School, February 21, 2000.

"How do the heart and lungs work." Hickory Hills Elementary School, Papillion, NE 20 February 2001.

"What is the Heart" Walnut Creek Elementary School, Papillion, NE, 20 February 2001.

Smoking and Other Recreational Drug Use. How to Respond to Peer Pressure and Just Say NO! Hickory Hills Elementary School, Papillion, NE 19 October 2001.

"How nutrition affects your heart and health." UNMC LIFeStyle Enhancement Center. 24 January 2002.

"How your heart and lungs work together and keep you healthy." 5th grade Hickory Hills Elementary School, Papillion, NE, 4 March 2002.

"What do your Heart and Lungs look like?" 3rd grade Walnut Creek Elementary School, Papillion, NE, 5 March 2002.

"What does your heart look like?" 3rd grade Hickory Hills Elementary School, Papillion, NE, 21 March 2002.

"Dissecting the Human Heart and Lungs. What do they look like and how do they work?" American Legion Post 32 and Mid America Council BSA, March 26, 2002.

"Stem Cell Research & Cloning: Should Cloning Be Legalized" Panel Discussion at the University of Northern Iowa, Cedar Falls, IA, 19 April 2002.

"Becoming an Author & How Your Heart Works." Third Graders at Walnut Creek and Hickory Hills Elementary Schools, Papillion, NE, 28 March 2003.

"Investigating How Your Heart and Lungs Work. Do you have one or two hearts?" Fifth Graders at Hickory Hills Elementary School, Papillion, NE, 4 April 2003.

"United We Stand" Tribute to US Military Personnel. With Video tape from Lee Greenwood (God Bless the USA) and letters of support from President George W. Bush and Vice-President Richard B. Cheney. 15 May 2003, Bellevue, NE.

"Understanding the risk factors of heart disease and their treatment." Dimensions in Clinical Medicine for Creighton Medical Students, Omaha, NE, 24 April 2003.

FH Washout protocol. The New Standard of Care coming from the Biggest little City in the World. Sierra Nevada Cardiology Associates, Reno, NV. 21 January 2009

Radio Interviews:

"For the Health of It!" Emergency Room Management of Acute Myocardial Infarction. The Cardiologists Perspective. KCFI Radio, January 28, 1994.

KFAB 1110 Radio, Omaha, NE, Interview with Gary Saddlemeyer and Mary O'Keefe, June 6, 1997.

KKCD FM/CD 105.9 Radio, Omaha, NE, Interview with Otis 12 and Liz Adams, June 20, 1997.

WMT Radio Interview, Cedar Rapids, IA, Mike Grim, July 17, 1997.

KCCK Radio Interview, Cedar Rapids, IA, Nancy York, July 17, 1997.

University of Northern Iowa, Public Radio Interview, Cedar Falls, IA, July 19, 1997.

University of Northern Iowa, Cedar Falls, IA, Presentation: "How to Bypass Your Bypass", July 19, 1997.

WHO AM talk radio 1040, Des Moines, IA, Interview, Jan Michelson, July 25, 1997.

KGBI 100.7 FM Interview, Omaha, NE, Heath Kramer and Jeff Kaiser, August 6, 1997.

KFOR 1240 AM Radio, Interview, Cathy Blythe, September 4, 1997.

KNSF News Talk Radio, Wichita, KS, Interview with Dr. Galichia and Kyle Grahm, September 6, 1997.

KCSR Radio, Chadron, NE, Interview with Celeste Lee - Part I, September 6, 1997.

KCSR Radio, Chadron, NE, Interview with Celeste Lee - Part II, September 9, 1997.

KMUW PBS Radio Station, Wichita, KS, Interview, Lou Stephens, September 11, 1997.

KCUR FM 89.3, University of Missouri - Kansas City, Kansas City, MO, Interview on "the Walt Bodine Show", Walt Bodine, September 17, 1997.

WIBW AM Radio, Interview, Topeka, KS, Sam Elliott, September 18, 1997.

KCMO Radio, Interview, Kansas City, MO, Russ Johnson, September 19, 1997.

KEFM K-Lite 96.1 FM, Radio Interview, "Outta Bed with Jack & Fred", Omaha, NE, September 22, 1997.

KGBI 100.7 FM, Interview, Omaha, NE, Heath Kramer and Jeff Kaiser, September 22, 1997.

KRTK FM 97.1 Radio, Interview, "America Talks Health", Dr. Keith Robinson, Houston, TX, October 3, 1997.

Crawford Broadcasting Systems, Syndicated Radio Talk Show, Irvine, TX, "Positron Emission Tomography for Heart Disease and Cancer", November 7, 1997.

KIOS 91.5 FM, UNMC Public Affairs National Public Radio Interview, Tom O'Connor, November 12, 1997.

Healthy Living, Nationally Syndicated Radio Talk Show, Fort Myers Florida, Dr. Brad Rachman, Three One Hour Interviews "Diet and Heart Disease", aired throughout Holiday Season December 1997 - January 1998.

KRTK FM 97.1 Radio, Interview, "America Talks Health", Dr. Keith Robinson, Houston, TX, April 3, 1998.

KRTK FM 97.1 Nationally Syndicated Radio Talk Show, Interview, "Heart Disease and What You Can Do About It", Dr. Keith Robinson, Houston, TX, July 22, 1998.

KRTK FM 97.1 Nationally Syndicated Radio Talk Show, Interview, "What Causes Heart Disease and Strokes", Dr. Keith Robinson, Houston, TX, August 5, 1998.

KRTK FM 97.1 Nationally Syndicated Radio Talk Program "America Talks Health", "Breakthroughs in Heart Disease" Dr. Keith Robinson, Houston, TX 23 January 1999.

KFAB AM 1110 Co-Anchor with Mary O'Keefe for Drive Time Radio, Omaha, NE, 11 February 1999.

KFAB AM 1110 Co-Anchor with Mary O'Keefe for Drive Time Radio, Omaha, NE, 11 February 1999.

"The Fleming Unified Theory of Vascular Disease and the American Diet." Here's to Your Health Syndicated AM Radio Talk Program with Deborah Ray and Dr. Carron. June 5, 2000.

"The Fleming Unified Theory of Vascular Disease and the American Diet." AM Radio Talk Program with Dr. Dennis Courtney, Pittsburg, PA. June 21, 2000.

"The American Diet and Heart Disease." AM Radio Talk Program with Dr. Dennis Courtney, Pittsburg, PA. July 17, 2000.

"High-Protein Diets and Heart Disease." Here's to Your Health Syndicated AM Radio Talk Program with Deborah Ray and Dr. Carron. October 19, 2000.

WBYU 1450 AM Talk Radio, "Diagnosis and Treatment of Heart Disease and Breast Cancer and the Impact of Diet." Bob and Jan Carr Show, New Orleans, LA, November 13, 2000.

"The Cheney Syndrome" Canadian Broadcasting Corporation. Dr. Brian Goldman. Healthnetwork, Toronto, Canada. July 2-6, 2001.

Breast Enhanced Scintigraphy Testing, Breast Cancer and It's Treatment. WTIx AM 690. Host Susan Burdicker 16 October 2001.

Vibrant Life Radio Talk Show with Drs. Tim Arnott and Diehl. 18 December 2003 Syndicated Radio.

The Debra Ray Show "Inflammation and Heart Disease" 5 January 2004 Syndicated Radio.

"How inflammation causes serious illness." By: Mike Carruthers of "Something you should know." 20 January 2004. Syndicated Radio.

The Frankie Boyer Radio Program "How diet affects heart disease through inflammation." 21 January 2004 - Syndicated Radio.

Dr. Tim Arnott Radio Program Life Talk Radio "Stop Inflammation Now!" 22 January 2004. Syndicated Radio.

Gary Null radio program "Inflammation and Heart Disease" 23 January 2004 Syndicated Radio.

WTAM AM talk radio with Bill Willis, Cleveland, OH, "Hidden Heart Dangers" 16 April 2004.

www.talknetradio.com, "Diets from 'A' Atkins to 'Z' Zone, Harvey S. Bartnof, MD, 25 May 2004.

WBAI-FM, New York, NY, "Stop Inflammation Now!" "Natural Living" The Gary Null syndicated radio program, February 3, 2005.

WROL-AM, WSRO-AM, Boston, MA, "Stop Inflammation Now!" "The Frankie Boyer Show", Syndicated radio program, February 4, 2005.

"Health Radio Network" "Dr. Mike's Look Younger, Live Longer Health Radio Show" February 5, 2005

WSRO-AM, Boston, MA, "Stop Inflammation Now!", "Frankie Boyer Show", February 7, 2005

1060-AM, Boston, MA, "Stop Inflammation Now!", "Frankie Boyer Show", February 7, 2005.

WGFS-AM radio "HealthLine" with Steve Aldridge, Atlanta, GA, February 7, 2005.

"Health Talk Radio", "The Deborah Ray Show", "Stop Inflammation Now!" February 8, 2005

CKLW-AM 800, Detroit/Windsor, ON, "The Health Report" with Melanie Deveau, February 14, 2005

KFCD-AM, Dallas, TX, "Stop Inflammation Now!", "The Kevin McCarthy Show", February 17, 2005.

WBAJ Radio, The John Sebastian Show, Detroit, MI, March 1, 2005.

WBCB-AM, "Family Matters" with Anthony Mustello, Philadelphia, PA, March 9, 2005.

CNN radio national, *espaniol*, "Inflammation and Heart Disease", with Maria Desax-Guerrero, March 9, 2005.

WWOW-AM, "Louie Free Radio Show", Cleveland, OH, March 21, 2005.

WEEU-AM, "Healthy Living with Nature's Garden" with Susanne Fiori, Reading, PA, March 21, 2005.

Marshall Radio, "PM Pages", with Liz Gunderson, Marshall, MN, April 4, 2005.

"The Beyond Health Show" with Raymond Francis, April 5, 2005
KYCY 1550 AM, San Francisco, CA
WWNN 1470 AM, Southeastern, FL
KMYL 1190 AM, Phoenix, AZ

"Your Second 50 Years in Radio Show" with Hedi Headley,
www.carefreepr.com/2nd50years.html, April 12, 2005
KKNT Phoenix, AZ
KLAV Las Vegas, NV
KAAA, KZZZ, etc.

WOR-AM radio, "Health Talk with Dr. Ronald Hoffman", New York/National,
April 12, 2005.

World Talk Radio (VoiceAmerica.com)/"Health Matters" with host Shoshanna
Bennett, www.worldtalkradio.com/archive.asp?aid=3908, April 16, 2005.

Creative Health & Spirit Radio Show, with Linda Mackenzie, Los Angeles, CA,
June 8, 2005.

KKOH 780 AM with Jim Fannin. Obama-Biden Transition Team Health Care
Discussion. December 22-28, 2008.

KUNR Public Radio with Danna O'Conner, Obama-Biden Transition Team
Health Care Discussion. December 22-28, 2008.

Television Interviews:

Channel 7, KETV Interview on Cholesterol, Omaha Nebraska, February 14, 1988.
Taken from Channel 7, KETV Interview on Cholesterol, Omaha, Nebraska,
February 13 - 17, 1989.

KTRK, Channel 13, PET Imaging, with Dr. James (Red) Duke, Houston, Texas,
February 17, 1991.

KTRK, Channel 13, Heart Rhythms with Dr. James (Red) Duke, Houston, Texas,
July, 15, 1991.

Channel 6, WOWT Interview on Treatment of Hyperlipidemias in the Elderly
Patient, Omaha, Nebraska, January 26, 1995.

KMTV 3 Television Interview with Trina Creighton, May 6, 1997.

KPTM FOX 42 Television Interview with Susan, June 13, 1997.

ABC News 8, Lincoln, NE - Linda Van Hoosen, June 22, 1997.

COX Cable Channel 23, Omaha, NE with Michael Braunstein, June 24, 1997.

WOWT Ch 6 - NBC Television, Omaha, NE with Sue Bagerly, July 7, 1997.

KGAN 2 Television Interview, Cedar Rapids, IA, Michelle Hall, July 17, 1997.

KWWL Ch 7 Television Interview, Waterloo, IA, Heather King, July 17, 1997.

WOI - TV 5 Interview, Des Moines, IA, Scott Smith, July 25, 1997.

WHO TV - 13 Interview, Des Moines, IA, Lori Graves, July 25, 1997.

KCCI TV - 8 Interview, Des Moines, IA, John Hoya, July 25, 1997.

KCTV CBS - Ch 5 TV Interview, Fairway (Kansas City), MO, Lori Tubbs,
August 1, 1997.

WOWT Ch 6 - NBC TV Interview, Omaha, NE, Sue Bagerly, August 5, 1997.

KETV Ch 7 Television Interview, Omaha, NE, Carol Klauss, August 7, 1997.

COX Cable Ch 23 Television Interview, Omaha, NE Michael Braunstein, August
11, 1997.

KMTV 3 Television Interview, Omaha, NE, Trina Creighton, August 13, 1997.

NBC Ch 5 Affiliate, Chicago, IL, Interview Program, Lisa Ripson, August 30,
1997.

KWCH TV - 12, Wichita, KS, Interview, Susan Arensman, September 12, 1997.

KAKE TV - 10 ABC Affiliate, Wichita, KS, Interview, Mike Luen, September
12, 1997.

KSNW TV - 3, Wichita, KS, Interview, Kathy Ivy, September 12, 1997.

KTKA 49 ABC Affiliate, Television Interview, Topeka, KS, Felicia Rolfe,
September 18, 1997.

KSNT TV - 27, NBC Affiliate, Interview, Topeka, KS, Jody Shields, September
18, 1997.

FOX 42 Television, Interview, Kansas City, MO, Mike Walter, September 19, 1997.

KPRC Ch 2 - TV, Interview, Houston, TX, Melissa Block, October 4, 1997.

KTVO - TV, Ottumwa, IA, Angela Height, October 10, 1997.

Cox Cable Public Access Ch 23, Omaha, NE, "Integrating Medicine and the 21st Century" - Parts I and II (2 hours), Michael Braunstein, November 4, 1997.

Cox Cable Public Access Ch 23, Omaha, NE, Interview "Heart Disease and Healthcare in the United States - Part I", Mary Matthews, November 18, 1997.

Cox Cable Public Access Ch 23, Omaha, NE, Interview "Heart Disease and Healthcare in the United States - Part II", Mary Matthews, December 2, 1997.

Cox Cable Public Access Ch 23, Omaha, NE, Interview "Heart Disease and Healthcare in the United States - Part III", Mary Matthews, December 16, 1997.

Cox Cable 23, "The Fleming Unified Theory of Vascular Disease" Host: Michael Braunstein, April 1999.

Fox 42 News, "Holiday Binging & Holiday Dieting", Omaha, NE, December 30, 1999.

Cox Cable 23, "The New Doctors" Host: Michael Braunstein, February 15, 1999.

The results of high protein diets on heart disease. Fleming Data presented at the request of Dr. Dean Ornish. **Good Morning America**, New York, NY, 7 August 2000.

"Diagnosing and Treating Heart Disease", Fox 42 News, Omaha, NE, August 18, 2000.

High Protein Diets and Heart Disease, **The Today Show** with Katie Couric, New York, NY, October 6, 2000.

Study sheds doubt on Atkins Diet, **MSNBC Home Page Segment**, New York, NY, October 6, 2000.

Channel 8, Documentary on Breast Cancer, New Orleans, LA, November 13, 2000.

"Breast Cancer" **Discovery Network Canada**. Original components filmed in June 2001. Sydney Suissa

"Breast Enhanced Scintigraphy Testing" PBS Special Part II Breast Cancer taping scheduled for Oct-Nov 2001 with Clara Wilkenson executive producer. Pending release filmed: 2002.

"Reversing the Aging Process. The Role of Diets and Heart Disease" Filming November 3, 2001 in San Diego, CA. Pending release filmed: 2002.

"Hidden Heart Disease. Could a simple, inexpensive test save your life?" **20/20 - ABC Network** 16 April 2004.

"Could simple heart test save your life?" **ABCNEWS.com** Q & A posting 21 April 2004.

Big Story: "Doctor holds health care discussion to help Obama." December 29, 2008.

Newspaper Articles:

TIMES Newspaper, Papillion Nebraska, Teresa Hoffman, June 4, 1997.

Lincoln Journal Star "Omaha doctor's heart book a cautionary tale." by David Swartzlander, June 21, 1997.

Omaha World Herald, Omaha, NE, Donnette Dunbar, June 30, 1997.

TIMES Newspaper, Papillion Nebraska, Teresa Hoffman, July 9, 1997.

TIMES Newspaper, Papillion Nebraska, "Papillion doctor's diet book can cut cholesterol." Teresa Hoffman, July 16, 1997.

Waterloo-Cedar Falls Courier, Waterloo, IA, "Heart Smart", Staci Schmit, July 16, 1997.

The Des Moines Register, Des Moines, IA, "The Cholesterol Connection", Melinda Voss, July 21, 1997.

Cedar Rapids Gazette, Cedar Rapids, IA, "Eating for a Healthy Heart", Elizabeth Kutter, August 4, 1997.

The Catholic Voice, Northeast Nebraska Newspaper, "Meet the Author", August 8, 1997.

Pitch Weekly Newspaper, Kansas City, MO, "Omaha doctor takes a different path in heart disease research." Patrick Dobson, August 21-27, 1997.

Pioneer Press, Glenview (Chicago), IL, Virginia Girst, August 30, 1997.

The Reader, Omaha, NE "How to Bypass Your Bypass", Michael Braunstein, September 4-11, 1997.

The Wichita Eagle, Wichita, KS, "Omaha doctor to talk about healthy hearts." Karen Shideler, September 9, 1997.

The Topeka Capitol-Journal, Topeka, KS, "The bypass bypass", September 15, 1997.

University of Northern Iowa (UNI) Special Report, Cedar Falls, IA, "Richard Fleming: teaching heart-happy living." September 24, 1997.

TIMES Newspaper, Papillion Nebraska, Local doctor to host healthy living seminar, September 24, 1997.

University of Northern Iowa (UNI) Special Report, Cedar Falls, IA, "Richard Fleming: teaching heart-happy living." September 24, 1997.

TIMES Newspaper, Papillion Nebraska, Local doctor to host healthy living seminar, September 24, 1997.

The Daily Nonpareil Newspaper, Council Bluffs, IA, "Heart of the Matter: Cardiologist tackles cholesterol head on." Carla Chance, October 6, 1997.

Ottumwa Courier, Ottumwa, IA, "Cardiologist to examine questions from the heart." Judy Kreiger, October 7, 1997.

Omaha Magazine, Omaha, NE, Article on Cholesterol, Nuclear Cardiology and Heart Disease, Jan Bass, January - February Issue 1998.

The Informer, "Heart of Learning", Papillion - LaVista, NE, Fall 1998.

The Reader, Omaha, NE "One for the Heart - What a Tangled Web We Weave", Michael Braunstein, February 11-17, 1999.

The Times, "Heart Smart: Local Doctor Has One-of-a-Kind Clinic", by: Jamie Nelson Hestermann, Papillion, NE, March 17, 1999.

Waterloo Cedar Falls Courier, Waterloo, IA, "Ex-resident using expertise to probe two diseases at once." EXCLUSIVE, by: Heather Lilienthal, April 22, 1999.

The Midlands Business Journal, "Early Diagnosis Prompts Opening of Fleming Institute", by: Wendy Clark, Greater Omaha, Lincoln (NE) and Council Bluffs (IA), Vol 25, No 17, April 30 - May 6, 1999.

Omaha World-Herald, "So Long Cigarettes", by: Kristi Wright, Omaha, NE, May 25, 1999.

"Nuclear Imaging: Helping to detect breast cancer"/"The debate over nuclear imaging." by Theresa Cha, The Lincoln Journal Star, Lincoln, NE, March 14, 2000.

"The New Doctors. Medicine Meets Healing on the Road to Health." by Michael Braunstein. Healing Arts Directory. March 15, 2000.

"Breast Cancer Update. Mammograms: Who Needs Them? Well, Maybe Nobody." by Michael Braunstein. Healing Arts Directory. March 15, 2000.

"High-Protein diet can hurt heart." by Theresa Cha, The Lincoln Journal Star, Lincoln, NE, August 6, 2000.

"Waterloo native sets the diet world on end." Meta Hemenway, Waterloo Cedar Falls Courier August 13, 2000.

"Doctor on 'Today' to take shot at fad diet." Meta Hemenway-Forbes, Waterloo Cedar Falls Courier October 5, 2000.

"Surprising study. Success in a controlled diet for local teens. by Ridgely Ochs, Newsday, Long Island, NY, October 13, 2000.

"Breast Cancer article" The Globe and Mail (**Canadian National Newspaper**) article by Mr. Paul Taylor (Health Editor). Original Interview June 27, 2001.

"Questions about stem cell issue dominate UNI panel discussion." article by Terry Hudson, Waterloo Daily Courier, April 21, 2002.

"Experts Declare Story Low on Saturated Facts." by Sally Squires, science writer for The Washington Post, August 27, 2002.

"Dieters charge Atkins led to heart ills." By: Reuters Press. MSNBC news. 20 November 2003.

"Area woman – Atkins diet has great risks." By: David Montero, Ventura County Star, Ventura, California, 3 January 2004.

"The Dynamic Duo" Stat Medicine Feature story. Lincoln Journal Star by Marc Andersen, 13 January 2004.

"The Heart Doctor Diet: Heart disease is Britain's biggest killer. Here, a top cardiologist reveals how a revolutionary detox can halt years of damage in just 7days." The Daily Mail, London, England, March 9, 2004.

"Defend against Britain's biggest killer." Life & Style (The London Web site of the year 2004). March 9, 2004.

"Eat to save your life." Daily Mail, by Michael Joseph, March 17, 2004.

"Anti-inflammatory Eating", The Washington Post, by Katherine Tallmadge, January 26, 2005.

"Detecting new risks for heart disease", The Los Angeles Times, by Shari Roan, February 28, 2005.

ABC News. Kellogg's Bad Apple Cartoon Causes Food Fight. Advocacy Group Says Cereal Ad is Misleading. By Michael Silverman, July 21, 2005.

ABC News Health. A Less-Fatty Big Apple? By Ryan Stanton, MD, September 27, 2006.

"Fire in your Arteries" by: Karen Ansel, RD, Best Life Magazine, February 16, 2007.

"Meetings set on Reno-area health care." By Frank X. Mullen, Jr. Reno Gazette-Journal. December 28, 2008.

"Forum set on health proposals: Freedom of Choice Act among discussion topics." By Frank X. Mullen, Jr. Reno Gazette-Journal. December 29, 2008.

"Northern Nevadans weigh in on national health-care reform." By Frank X. Mullen, Jr. Reno Gazette-Journal. January 4, 2009.

Non-medical Journal Reports/Magazines:

"Taking Diet to Heart" Today's Health and Wellness Magazine. by: Susan Perry Jan/Feb 2001.

"Your Ready to Start Exercising: Is Your Heart?" Today's Health and Wellness Magazine. by: Susan Hawthorne May/June 2001.

"Your big new threat: Inflammation" USA Weekend. By: Jean Carper. 9 March 2003.

"Can Fat be Good for You?", by: Janis Graham, Good Housekeeping, August 2003.

"Anti-inflammation Diet: A cure wrapped in plants." Today's Health and Wellness Magazine. By: Lynn Madsen. Jan/Feb 2004.

"Vital & Fit: The latest on cancer prevention." Let's Live. By: Vera Tweed. February 2004.

"Stop Inflammation Now!", New Living Magazine, New York, New York, 9 April 2005. www.newliving.com

"Health know-how. Cellular inflammation." First for Women Magazine, 23 May 2005.

Self Magazine article on Inflammation, February of 2006.

Big Brains Cutting-Edge Medical Technologies. Raising the Standard of Care: Northern Nevada's Medical Technology. By: Jennifer R. Baumer. RLife Magazine. February 2009.

Medical Journal Reports:

"Time to rethink angina, role of SPECT imaging. by Conni Ford Bergmann, Cardiology Today, 2000;3(7).

Preventive Cardiology: "High-protein diets may lead to CAD progression." by Conni Ford Bergmann, Cardiology Today, 2000;3(11):42.

"Diet and Nutrition in Your Practice. Cautioning Patients about Extreme Diets." by Charlotte LoBuono. Patient Care, 2001;Aug 15, 28-46.

"Nuclear Medicine Fits Bill for Problem Breast Diagnosis: Scintimammography and PET show Promise for Detecting Primary Cancer, Recurrence, and Metastasis. Breast Enhanced Scintigraphy Testing" Diagnostic Radiology Imaging. Speical Session by: Karen Sandrick, 2001;Sept: 49-52.

"Non-invasive assessment of heart disease." Diagnostic Radiology Imaging. December 2001.

"New Research Supports Whole Soy's Role In Breast Health" Dr. Christiane Northrup's Health Wisdom for Women. June 2002, 9:6-8.

"Novel Imaging Technique Reveals Breast Benefits of Soy Supplementation." by Erik L. Goldman (editor-in-chief). Holistic Primary Care April 15, 2002; pp. 1 and 6.

"Why the confusion about low- and high-fat diets?" by Richard M. Fleming, MD, special to Today in Cardiology. Cardiology Today 2002:5(9):26.

"Best Case" American Society of Nuclear Cardiology: Imaging Update. January 2009:4.

PRESENTATIONS AT HOSPITALS AND MEDICAL CONFERENCES:

Cardiopulmonary and Trauma Instructor, University of Iowa College of Medicine Freshman and Sophomore Classes on Emergency Medicine, Iowa City, Iowa 1981 - 1983.

Faculty for Basic Life Support Classes for Hospital Staff and Employees (Physicians, Residents, Nurses and Ancillary personnel), University of Iowa Hospitals and Clinics, Iowa City, Iowa, 1983 - 1986.

Faculty for Advanced Cardiac Life Support classes, University of Iowa Hospitals and Clinics, (Physicians, Residents, Nurses and Ancillary personnel), Iowa City, Iowa, 1985 - 1986.

Faculty for Advanced Cardiac Life Support classes, Residents in Internal Medicine, Surgery, Family Practice and Pediatrics, Des Moines, Iowa, 1986 - 1987.

Development and Institution of the Cardiopulmonary Rehabilitation Risk Factor Modification and Cardiopulmonary Stress Testing Program with Dr. Francisco Fuentes, Hermann Hospital, Houston, Texas, 1989 - 1990.

Presentation of Atrial Fibrillation, It's Causes, Symptoms and Treatment. *For Hermann Hospital's Children's Miracle Network Telethon*. Donation by Marion-Merrell Dow Pharmaceuticals, May 1992.

Nuclear Cardiology, **Grand Rounds** at St. Luke's Hospital, Cedar Rapids Iowa, August 27, 1992.

Interpreting Results of Coronary Arteriography. Sartori Hospital, Cedar Falls, Iowa March 9, 16, and 30, 1994.

Sartori Health Notes "Home Safe Home" A Publication for Sartori Works Clients, Sartori Memorial Hospital, July 1994.

"Angina" Erhling Berquist Hospital, USAF (SAC), Omaha, Nebraska January 1995

"What to Expect in the Treatment of Hyperlipidemia." **Grand Rounds**, Bergan Mercy Hospital, 11 April 1995.

"Cardiac Risk Factor Update: How to Bypass Your Bypass." Creighton University Family Practice Department **Core Lecture**, January 6, 1998.

University of Nebraska Medical Center (Omaha, Kearney, Grand Island & Plattsmouth). Family Practice **Grand Rounds**. "The Role of Diet in Prevention of Coronary Artery Disease." January 21, 1998.

"The Pathogenesis of Vascular Disease" Primary Care Physicians, Sioux Falls, SD, September 24, 1998.

"The Role of Lipids in the Pathogenesis of Vascular Disease", *Invited Lecturer* for the 16th Annual North Central Heart Fall Symposium, September 25, 1998.

"Noninvasive Assessment of Heart Disease in Women." First Annual Heartland Chapter Symposium. Alegent Health Bergan Mercy Medical Center, April 24, 1999.

"Fleming Unified Theory of Heart Disease" Erhling Berquist Hospital, USAF (SAC), Omaha, Nebraska. 2 September 1999.

"Nuclear Cardiology: When and How to Use It to Take Care of Your Patient", Erhling Berquist Hospital, USAF (SAC), Omaha, Nebraska, 8 October 1999.

"Dual Use Procedure for Detecting Breast Cancer and Heart Disease" Erhling Berquist Hospital, USAF (SAC), Omaha, Nebraska. 4 January 2000.

"What is Nuclear Cardiology?", Omaha Chapter of Professional Coders, 18 January 2000.

"Nuclear Cardiology - The New Millenium" Erhling Berquist Hospital, USAF (SAC), Omaha, Nebraska. 28 January 2000.

"Is the patients chest pain due to angina? The role of Nuclear Cardiology" The 51st Annual Conference for the North Dakota Society of Radiologic Technologists (NDSRT) and the American College of Radiologists (ACR). Fargo, ND. 28 April 2001.

"The Pathogenesis of Vascular Disease" The Fifth Annual International Congress of BioEnergetic Medicine. Orlando, Fl. May 26, 2001.

"Case Examples of Treating Heart Disease" The Fifth Annual International Congress of BioEnergetic Medicine. Orlando, Fl. May 26, 2001.

"Breast Enhanced Scintigraphy Testing (B.E.S.T.): Increased Accuracy in Detecting Breast Cancer Accomplished by Combining Breast and Cardiac Imaging" **Reading with the Experts Presentation.** 48th Annual Scientific Sessions for the Society of Nuclear Medicine, Toronto, Ontario, Canada. June 26, 2001.

"Myocardial Perfusion Imaging Using High-Dose Dipyridamole (HDD) Defines Angina: The Difference Between Coronary Artery Disease (CAD) and Coronary Lumen Disease (CLD)" **Reading with the Experts Presentation.** 48th Annual Scientific Sessions for the Society of Nuclear Medicine, Toronto, Ontario, Canada. June 27, 2001.

"Breast enhanced scintigraphy test (B.E.S.T.) demonstrates improvement in breast inflammation in women consuming soy protein." **Invited Presenter** at the 4th International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. San Diego, CA, USA 4 November 2001.

"How diet influences diabetic risk factors for heart disease, including triglycerides, homocysteine and (TG/HDL) insulin resistance. 8th Annual Diabetes Expo, Phoenix, AZ, 1 May 2004.

"How do popular diets influence cardiovascular risk factors." Cardiac catheterization conference, University of Colorado Health Sciences Center, 4 May 2004.

"How do popular diets influence cardiovascular disease risk factors." Keynote lecturer for The Pritikin Center, 6 May 2004.

"Carbohydrates: A Simple and Complex Problem. How diets of varying carbohydrate content influence weight loss and the INFLAMMATORY CVDRFs responsible for coronary artery disease. 1st Nutrition News Forecast for the American Dietetic Association, Chicago, IL, 13 May 2004.

"Examining Heart Disease and Obesity: Does Treating One Automatically Treat the Other." Cardiovascular Disease Grand Rounds, University of Iowa College of Medicine. 1 December 2004.

"Can Dieting and Exercise Break the Cycle of Obesity, Inflammation and Heart Disease?" University of Missouri-Columbia Cardiology Conference, Columbia, MO, 22 June 2005.

What is MPI and When Should I Order It? Reno VAH Noon Conference, Reno, NV, 10 August 2005.

Non-invasive Cardiology for Medical Students: Understanding Echocardiography and Nuclear Cardiology. University School of Medicine, Reno, NV, 26 August 2005.

Reading Electrocardiograms. A Lecture Series: What can they tell us about the patient? Reno VAH/Univ. School of Med Reno, Internal Medicine, Noon conference. Reno, NV, 15 March 2006.

Echocardiography. What Does the Nurse Practitioner Need to Know? 25 April 2006.

Acute Coronary Syndromes and Electrocardiograms. Internal Medicine CME conference, CIHVAH, Des Moines, IA, 11 July 2007.

Advancements in Nuclear Cardiology: Sequential Imaging Unmasks Vulnerable Plaque, Internal Medicine Residents Conference, Renown Medical Center, Reno, NV, 12 June 2008

'Sequential Stress Imaging Unmasks CAD Missed by 60 Minute Imaging Only: How to More Accurately Find Your Patients Heart Disease.' Kneibert Clinic, Poplar Bluff, MO 22 August 2008.

'Blumgart and Fleming-Harrington. Why Sequential Imaging is More Important in the Detection of Heart Disease than Single Imaging Only Following Stress.' Board Room, Poplar Bluff Regional Medical Center. Poplar Bluff, MO. 27 August 2008.

FH Washout Protocol. The New Standard of Care coming from the Biggest Little City in the World. Renown Medical Center, January 21, 2009.

Multiple SPECT Images at 5 and 60 Minutes Following Stress are Critical in Clinical Decision Making! Poplar Bluff Education Symposium, Cape Girardeau County Area Medical Society. Poplar Bluff, MO, February 21, 2009.

SPECIFIED LECTURES

IMPACT Communications, Inc. Hypertension in the Older Patient: Integrating New Guidelines into Clinical Practice (Pfizer), March 1998 - April 1999.

American Heart Association, Nebraska - Speaker's Bureau 1996 - 1999.

The Importance of Treating Both Hypercholesterolemia and Hypertriglyceridemia. (Abbott) - April 1998 - Present.

Faculty Lecturer "the Treatment of Hypercholesterolemia or mixed dyslipidemia".
(SmithKline Beecham) August 1998 - Present.

Faculty Lecturer "Hypercholesterolemia and Lipid-Lowering Therapy (Novartis)
November 1998 - 2000.

Invited Speaker for the Society of Nuclear Medicine (Molecular Imaging)
Speakers Bureau, 19 March 2008 - Present.

MODERATOR AND GOVERNMENT EVENTS

Obama-Biden Transition Team, Health Care Community Discussion, Reno,
Nevada, December 29, 2008.

PEER REVIEW MEDICAL JOURNAL Reviewer, editor and grant reviewer

Contributing Editor for the *American Journal of Physiologic Imaging*, 1992-1993.

Cardiology/Nuclear Cardiology Reviewer *Mayo Clinic Proceedings* 1997 -
Present.

Member of Editorial Board, *International Journal of Angiology* May 1997 - 2002.

Member of Editorial Board, *HeartDrug*, December 1999 - 2000.

Lancet Reviewer, 2002 – Present.

Angiology, the Journal of Vascular Disease, Editorial Board/Reviewer, 2002 –
Present.

Member of World Association of Medical (WAME) Editors, 2002 – Present.

The Journal of Nutrition, 2003 – Present

Circulation, 2004 – Present

U.S. Department of Health and Human Services, Health Resources and Services
Administration, Grant Reviewer for Cardiovascular Critical Care, Cancer, and
Nutrition. 2006 -Present.

Stroke, 2006 – Present.

Journal of Cardiovascular Pharmacology and Therapeutics, 2008 – Present.

Evidence Based Complementary and Alternative Medicine (ecam), 2009 –
Present.

The American Journal of Medicine, 2009 – Present.

The Journal of Nuclear Medicine, 2009 – Present.

The International Journal of Cardiology, 2009 – Present.

Reviewer AND editor FOR Non-medical journals

NON-MEDICAL Journals

Contributing writer for *Strictly Health*, *Strictly Business*, and *Strictly Women*, Lincoln, NE 1997.

Member of Medical Advisory Board for Today's Health and Wellness Magazine, December 2000- Present.

RESEARCH Grants AND STUDIES

Teboroxime research project with SPECT Imaging, Squibb Diagnostics, 1989-1992.

Parke-Davis Phase IV Clinical Investigator for the "ADOPT Study" 1991 - 1992.

Phase IV Studies with Norvasc 1992 - 1993.

Phase III Trials "The Safety and Efficacy of Cardizem CD for the Treatment of Stable Angina Pectoris" 1992 - 1993.

The Evaluation of CardioTec Resting Washout in Comparison to 201-Thallium in Patients Scheduled for Coronary Arteriography. 1993

GUSTO Investigator in Iowa, 1992 - 1994

PAREXEL Alive (AzimiLide Post Infarct SurVival Evaluation Trial) study
Principal Investigator 1998 - 1999

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12 August 2009

Dear Richard:

You inquire about my analysis of your data and of the Hansen data. Neither was ever provided to you. Using well established methods I made multiple **fabrication** tests of your data. There was no evidence of **fabrication**. Drs. Carriquiry and Kaiser used complex methods for detecting **fabrication** recommended by the Government agency responsible for developing such methods and for overseeing their use in PHS agencies. They found no evidence of **fabrication**. I found the Hansen data were **plagiarized**, as later confirmed in Court. I found the Hansen data to be **falsified**, as later confirmed in Court. The law establishes three forms of data fraud: **fabrication**, **falsification**, and **plagiarism**. You were charged with **fabrication** and all the tests show there was no **fabrication**.

It may be best to provide some commentary on my statistical background. My prewar experience had been high school dropout to take a manufacturing production line job. It was the depths of the Depression. We were on welfare. Night school (Electrical Engineering, Georgia Tech) led to employment in the Electrical Engineering departments of a power company and then a telephone company. My professional involvement with statistics began with my first job upon returning from three years WWII Naval service. It was at Georgia Tech doing statistical analyses for corporate studies in industrial psychology in the Psychology Department, the beginnings of my involvement in psychology. The following year brought an appointment to the Mathematics faculty. In 1949-50 I became a student in a one-time applied statistics program at Yale, taught by the world's top statisticians as visiting professors. It was my good fortune to be assigned as a graduate assistant to Sir Ronald Fisher, universally regarded as the greatest statistician of all time. Not only was Fisher the Father of modern statistics, he was also the Father of modern population (quantitative) genetics which is how I got into neuro-behavioral genetics. Also on the visiting faculty were Frederick Mosteller and Philip Rulon of Harvard. Many regard Mosteller as the greatest statistician of the second half of the 20th century. Rulon held the Measurement chair at Harvard. In 1951 I went to Harvard as a post-doc with Mosteller and also worked in a Harvard affiliated research institute led by Rulon and American Association for the Advancement of Science President Kirtley Mather. There I was Project Director on two contracts, one in air traffic control for the Air Force, the other for simulator tactical combat training for flag rank Naval officers. Next was a research consulting slot with the State of Connecticut for educational and labor market studies. I held various professional offices, most interesting being the Presidency of the Connecticut Chapter of the American Statistical Association. Connecticut had a high population of insurance statisticians (actuaries) as the Insurance State, of industrial statisticians (quality control engineers) as the high tech manufacturing center where mass production originated (clocks and arms), and of financial statisticians (accountants) as the leading commuter residential State for the New York banking industry. Two of my Executive Committee went on to Nobel Laureates in Economics (Tobin and Koopmans). I also served on an Institute of Mathematical Statistics Committee on Standards for Training of Statisticians. My career moved to academe in 1957 where I formally retired in 1986. I was named Distinguished Scholar at the University of Northern Iowa. I have been a regular reviewer for a number of scientific journals here and in Europe and for the National Institutes of Health and the National Science Foundation. After over two decades of retirement I have been accepting review requests less frequently.

You contacted me for advice on an indictment charging that "some of the data were fabricated" in a soy chip diet study of 60 research participants. More specifically you indicated it was known that some of the data were genuine but alleged later data were fabricated. I replied fabrication of data is a matter of great current interest in the financial community, the intelligence community, and the health research community. My advice was that you should contact the Office of Research Integrity to ascertain what, if any, assistance you could obtain from them. They were established as the Federal Agency responsible

for developing methods for detecting lack of integrity in research data and were touted in the statistical world for their contributions. They inherited some of the FBI experts in data fraud but early reports on formation of the ORI were not clear on the scope of their mission which was asserted to be Government wide on data fraud research and education but limited to PHS activities in investigatory authority. Your attorney did not see me as a potential witness and my suggestion was Dr Alicia Carriquiry who has a high reputation and who teaches forensic statistics at Iowa State University whose Statistical Laboratory has long been regarded as one of the top half dozen statistical institutes in the world.

You told me your attorney regarded statistics as worthless in the courtroom and any good lawyer could destroy statistical evidence. I commented my accountant brother who is operating vice-president of a financial house and on multiple boards of directors would be horrified to learn that any good lawyer could destroy the results of any audit. You indicated you were advised by your attorney that the judge held similar negative views of statistics. I am skeptical. My experience has been of lawyers trying to make statistics sound worthless only to have the judge chastise them with a lecture on statistics. My experience is not extensive but I have testified a few times. According to the Des Moines Register many years ago I was the witness who brought regression analysis into the judicial system as a standard method for assessing race and sex discrimination in wages and salaries. Some of the lawyers betrayed little competency in statistics. The judges I have encountered were more knowledgeable. When I expressed surprise once after trial at how much the judge knew he commented it was the job of judges to learn what they needed to know and he had obtained a crash education in statistics because he was the judge who heard the great redistricting case.

The difficulty with statistics is that a type of reasoning is required to which people are not accustomed. The fundamental basis of statistics is that the universe is governed by the laws of chance. The less scientifically educated can be misled, as your attorney suggests, by the fact the statistician will not say with certainty that something is or is not so. The statistician's work is based on the fact there is no certainty. That reality is expressed in the judicial system by the abstraction of levels of chance: "beyond a reasonable doubt" and "preponderance of the evidence". There are studies on the levels of chance people ascribe to these terms. I have seen appeals court decisions remanding for failure to include the quantitative levels of probability in the court record. In the abstract we may identify a connection and prove *if A then B* but in the real world the exact proof is that *if A then B plus or minus e*. In popular parlance there is a margin of error. Statisticians are by the nature of their profession aware of error where most people are not. For example, people tend to think of computers as giving unquestionable calculations. However *A times B equals C* is actually *A times B equals C plus or minus e*. The margin of error is small but real. Forty years ago the National Bureau of Standards developed very complex algorithms for very simple arithmetic operations such as multiplication for the purpose of reducing that margin of error (*NBS Special Publication 339*, 1970). Other algorithms verified error levels in very complex calculations. I still use them occasionally and decry their absence from contemporary software packages.

The detection of research fraud rests on three basic scientific realities. The universe is governed by the laws of chance, hence we can test whether data follow the laws of chance or are fabricated. The phenomena of the real world result from many factors interacting with each other. The National Transportation Safety Board needs months to run down the specific factor or factors leading to a crash. The Mayo Clinic may run a hundred tests to discover why a body is not functioning properly and additionally consider their relationships to each other. Physiology and behavior vary statistically with differing genes and environment. To avoid detection the fraud perpetrator must be able to anticipate which tests and which interrelationships will be tested and design data which will pass those tests. The

third and never mentioned fact is that Pavlovian conditioning and operant conditioning were displaced by the discovery about half a century past that the human nervous system cannot manage ten concurrent concepts. Our air safety research revealed that airplane accidents stemmed from too much information—one can tell time more readily with a four number otherwise blank dial than with a face showing 60 tick marks. Weather maps went from detailed measures and locations to five or at most six-color displays. The keep-it-simple principle was born.

You sent me your data as being effects of a dietary soy supplement in a sample representative of U.S. adult males and females selected for obesity. It was alleged earlier participants were real but later ones were fabricated. This fitted the paradigm of standard industrial quality control. Quality control engineers test and statistically track products monitoring whether products show trends away from statistical expectations and specifications. Trends or deviations signal underlying production factors have changed leading the engineers to investigate to determine what changed and to correct the problem. The allegation that the underlying factors changed from dieter response to fabrication seemed a perfect fit. For three quarters of a century it has been conventional to display the statistics in the form of charts showing the sequential measurements and boundaries of expected margins of error. The methods originated with W. Edwards Deming (one of the Fathers of survey and census methods and the progenitor of Japanese manufacturing production and quality control methods) and with Walter Shewhart for whom the charting method is named. I tested your data and found no evidence of changes in the data, hence, no evidence of fabrication. For reasons cited above that fabrication is very difficult and because Shewhart charting has long been well established and successful as the basis for quality control I concluded there was no evidence of fabricated data. You forwarded my assessment to your attorney, Mr. Hansen.

Mr. Hansen wrote me it is impossible to tell whether data are fabricated on the basis of examining the data. (I was tempted to point out the recent major fraud cases in which the primary evidence was the CPA audits.) He indicated he could easily fabricate data so that it could not be detected. He indicated he would do so and send me a data set comparable to yours and challenged me to use my Shewhart methods to show his data were fabricated. He particularly emphasized that he had written an undergraduate thesis on Deming and fully understood the concept. As I recall there was an e-mail explicitly stating the issue was that earlier data were valid and the balance of the data were not.

I tested the Hansen data set as I would as a journal reviewer. I reported that the first three tests each showed data were falsified or, more precisely as a journal reviewer, they were not what they were represented to be. Specifically the results showed the data were not representative of the population to which inferences were to be made. For journal reviewing I would have stopped at that point, rejecting the manuscript and leaving it to the Editor to decide whether to investigate it as falsification or conclude the sampling procedures were defective.

As requested I did apply the Shewhart methods and reported to Mr. Hansen they showed no fabrication. Since he had clearly stated he understood the method would test whether some of the data were genuine and the balance fabricated, since he had prepared the data, and since the data tested as not being fabricated, it was evident he knew the data were not fabricated. It seemed impossible Mr. Hansen could have obtained such data elsewhere so the data must be falsified Fleming data. A plagiarism test was statistically significant in the range of seven orders of magnitude. In layman's terms the chances the Hansen data were not plagiarized from the Fleming data are less than one in ten million or of the same order of magnitude as the chances that one of the jurors will die in an automobile accident in the next 24 hours. I saw no need for further plagiarism tests. At the time I concluded Mr. Hansen's intent was to test my analysis of the Fleming data to see if I arrived at a different conclusion when I was led

to believe the data were fabricated. We communicated no further.

In all I made nine fabrication tests on the Fleming data and nine on the plagiarized Hansen data. None of these 18 tests showed any evidence of fabrication. All three falsification tests showed the Hansen data had been falsified. The plagiarism test speaks for itself. Fabrication, falsification, and plagiarism are the three forms of health data fraud defined by statute.

The Carraquiry-Kaiser report represents a totally different approach than mine. It follows along the lines suggested by the Office of Research Integrity. The ORI is the Governments agency for developing best methods for detecting research misconduct which would seem to establish its methods as a Government established standard.

I note, inter alia, that the Carriquiry-Kaiser report speaks of difficulties with the Hansen report which also arose at Trial. My reading of the report is that the authors were puzzled by the Hansen report because they could find no evidence of fabrication when they were told the data were fabricated. They explicitly excluded falsification tests, justified by that information but which I regarded as something of a deficiency.

I do not have readily available all of the Shewhart charts nor the plotting programs which generated them. Attached are work copies not fully labeled. On the density plots the header is not a label but part of the computer program which generated the graphic.

In summary I audited the Fleming data using a number of standard industrial quality control tests to determine whether some of the data were genuine and some fabricated. There was no evidence of fabrication. I similarly audited the Hansen data finding no evidence of fabrication. I applied several tests to see if the data were representative of the defined population group. The Fleming data were. The Hansen data were not, suggesting falsification. A comparison test showed the Hansen data were plagiarized from the Fleming data. Falsification tests rest on the effects of a large number of underlying factors. Falsifying the numbers for a few of those factors alters little of the underlying factor effects. The assessment of no evidence for fabrication of research participants in the Hansen data simply provides a confirmation of lack of evidence of fabrication of research participants. The Carriquiry-Kaiser report/testimony represent an entirely different and more complex set of tests for fabrication following the recommendations for testing for fabrication of the Federal agency charged with developing and promulgating such testing methods. With their entirely different approach from mine they also found no evidence of fabrication of the Fleming data and confirmed that result with the Hansen data. For report and testimony they were asked to respond only to the charge of fabrication. They were not asked to test for either falsification or plagiarism and did not do so.

As I said at the beginning: Using well established methods I made multiple **fabrication** tests of your data. There was no evidence of **fabrication**. Drs. Carriquiry and Kaiser used complex methods for detecting **fabrication** recommended by the Government agency responsible for developing such methods and for overseeing their use in PHS agencies. They found no evidence of **fabrication**. I found the Hansen data were **plagiarized**, as later confirmed in Court. I found the Hansen data to be **falsified**, as later confirmed in Court. The law establishes three forms of data fraud: **fabrication**, **falsification**, and **plagiarism**. You were charged with **fabrication** and all the tests show there was no **fabrication**.

Using exponentially weighted moving average (EWMA) charts

Control charts are specialized time series plots, which assist in determining whether a process is in statistical control.

By Keith M. Bower

Some of the most widely-used form of control charts are \bar{X} -R charts and Individuals charts. These are frequently referred to as "Shewhart" charts after the control charting pioneer Walter Shewhart¹ who originated such techniques. These charts are sensitive to detecting relatively large shifts in the process, i.e. of the order of 1.5σ or above.

Two types of charts are primarily used to detect smaller shifts, namely Cumulative Sum (or CUSUM) charts and Exponentially Weighted Moving Average (EWMA) charts. E.S. Page² (1954) originally developed the CUSUM chart.

A CUSUM chart plots the cumulative sums of the deviations of each sample value from a target value. It has been used in various industries (especially the chemical industry) and the form of the CUSUM has been refined over the years to further increase its sensitivity (e.g. the Fast Initial Response, or FIR technique³).

Alternative technique

An alternative technique to detect small shifts is to use the EWMA methodology - developed by S.W. Roberts⁴ in 1959. This type of chart has some very attractive properties, in particular:

1. Unlike \bar{X} -R and Individuals charts (without the Western Electric Handbook⁵ rules which aim to increase sensitivity), all of the data collected over time may be used to determine the control status of a process.
2. The EWMA is often superior to the CUSUM charting technique for detecting "larger" shifts.
3. EWMA schemes may be applied for monitoring standard deviations in addition to the process mean.
4. There exists the ability to use EWMA schemes to forecast values of a process mean.
5. The EWMA methodology is not sensitive to normality assumptions.

¹ Shewhart, W.A. (1931). *Economic Control of Quality of Manufactured Product*. Van Nostrand-Reinhold, New York.

² Page, E.S. (1954). "Continuous Inspection Schemes." *Biometrika*, Vol. 41, No. 1.

³ Lucas, J.M., Crosier, R.B. (1982). "Fast Initial Response for CUSUM Quality Control Schemes." *Technometrics*, Vol. 24.

⁴ Roberts, S.W. (1959). "Control Chart Tests Based on Geometric Moving Averages." *Technometrics*, Vol. 1.

⁵ Western Electric (1956). *Statistical Quality Control Handbook*. Western Electric Corporation, Indianapolis, IN.

An important assumption that underpins the use of the EWMA (as well as other control charts) is that the samples obtained over time be independent. If that assumption is violated, there are two possible scenarios⁶:

- a. Positive autocorrelation (e.g. low values tend to be followed by other low values, or high values tend to follow other high values). This can possibly lead to control limits that may be too narrow - positive correlation can increase the frequency of false alarms.
- b. Negative autocorrelation (e.g. processes that frequently over-correct) may lead to overly wide control limits; hence special causes of variation that may be present in the process could be missed.

Consider the following simulated time series where the response variable is the concentration of an active chemical, expressed in grams per gallon.

Each individual batch takes several hours to be produced; hence analysis on the individual values may be appropriate. Suppose that we have knowledge of our process, namely that the historic mean is 20 grams/gallon and the within-subgroup standard deviation is 1 gram/gallon.

Underlying distribution

Using the first 30 observations to provide an estimate as to the possible underlying distribution, we note from Fig. 1 that the null hypothesis of normality cannot be rejected at the $\alpha = 0.10$ significance level, as the p-value of 0.420 associated with the Anderson-Darling test is greater than 0.10.

Note that Individuals control charts are more sensitive than \bar{X} charts to the normality assumption. As Montgomery⁷ states, "Even in situations where the normality assumption is violated to a slight or moderate degree... [Shewhart]...control charts will still work reasonably well." Though, as was noted by Schilling and Nelson⁸, for subgroup sizes of less than 4, non-Normality can lead to serious problems (in particular, a high false alarm rate). Importantly, the EWMA structure is insensitive to Normality, whereas CUSUM charts are sensitive to Normal assumptions⁹. This makes the EWMA chart an attractive candidate in general when addressing small changes in a process.

Checking the autocorrelation function (ACF) results in Fig. 2, there does not appear to be a problem with the assumption of independence for the first 30 observations, as the ACF statistics fall inside the 95% confidence band.

⁶ Montgomery, D.C. (1996). *Introduction to Statistical Quality Control, 3rd Edition*. John Wiley & Sons.

⁷ Montgomery, D.C. (1996). *Introduction to Statistical Quality Control, 3rd Edition*. John Wiley & Sons.

⁸ Schilling, E.G., Nelson, P.R. (1976). "The Effect of Non-Normality on the Control Limits of \bar{X} charts". *Journal of Quality Technology*, Vol. 25.

⁹ Hawkins, D.M., Howell, D.H. (1998). *Cumulative Sum Charts and Charting for Quality Improvement*, Springer-Verlag, New York.

As Fig. 3 shows, the Individuals chart (using the 3σ rule only) for the original 30 observations with 10 further observations after a 1σ shift has occurred indicates that the process is in statistical control. However, as indicated earlier, it should be noted that Individuals charts are not sensitive to small shifts in the process mean.

An EWMA chart may be used to detect small shifts. The parameters used are a constant (r) and some multiple (k) of the estimated value of σ . The EWMA for individual values may be defined as:

$$Z_i = rX_i + (1 - r)Z_{i-1} \text{ where } 0 < r \leq 1, i = 1, 2, \dots, n, n+1, \dots$$

Note that the average of some preliminary data (\bar{X}) is sometimes used for Z_0 . Here we use $Z_0 = 20$ and the MINITAB default values of $r = 0.2$ and $k = 3$. Note that values of $r = 1$ and $k = 3$ are used in the regular Shewhart control charting methodology.

Small shifts

As the EWMA chart in Fig. 4 indicates, the process exhibits an out-of-control situation after the 38th data point. Importantly, this shift of 1σ , initiated after the 30th observation, was not detected using the Individuals control chart.

In conclusion therefore, one finds that EWMA charts are more sensitive than regularly used control charts to detect small shifts in a process. The non-necessity of Normally distributed data weighs in favor of the EWMA over the CUSUM, though as with all control charts, the assumption of independent subgrouping ought to be investigated.

Keith M. Bower is a technical training specialist with Minitab Inc., State College, PA, USA. www.minitab.com.

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Figures

Fig 1

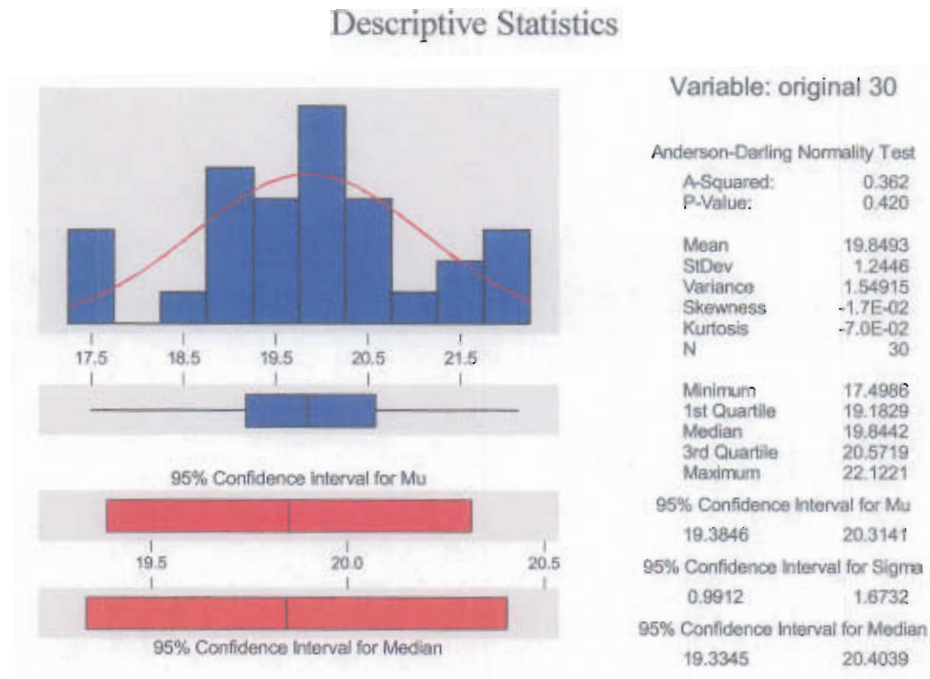


Fig 2

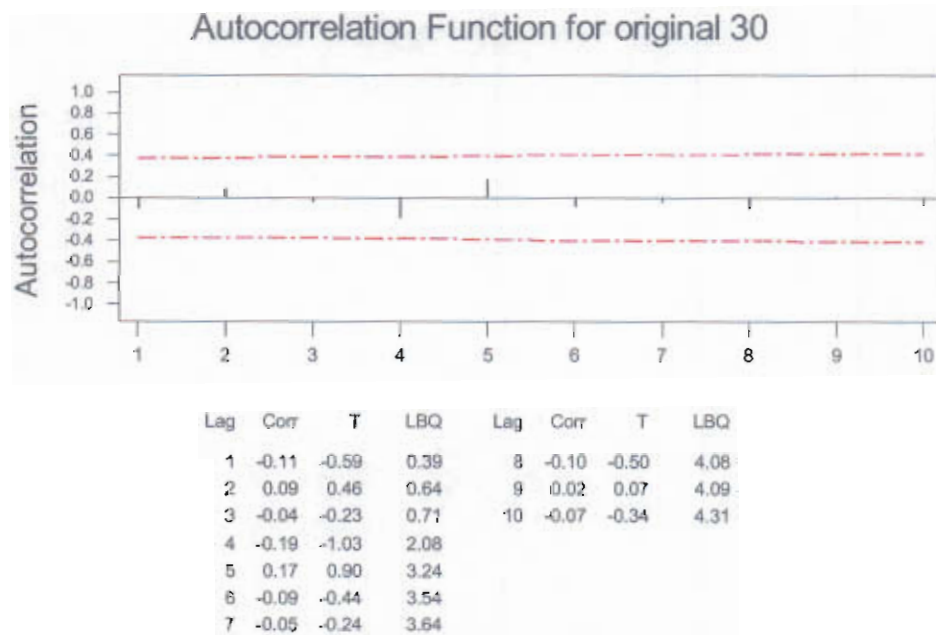


Fig 3

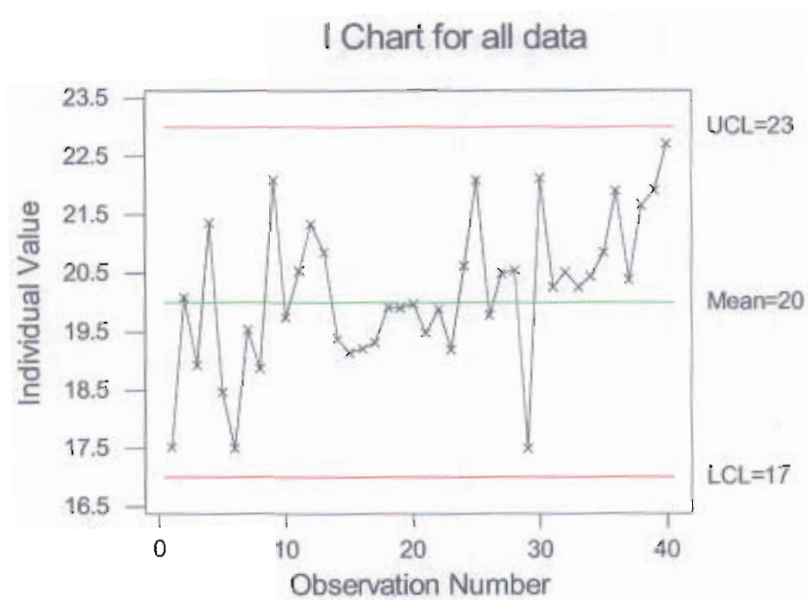
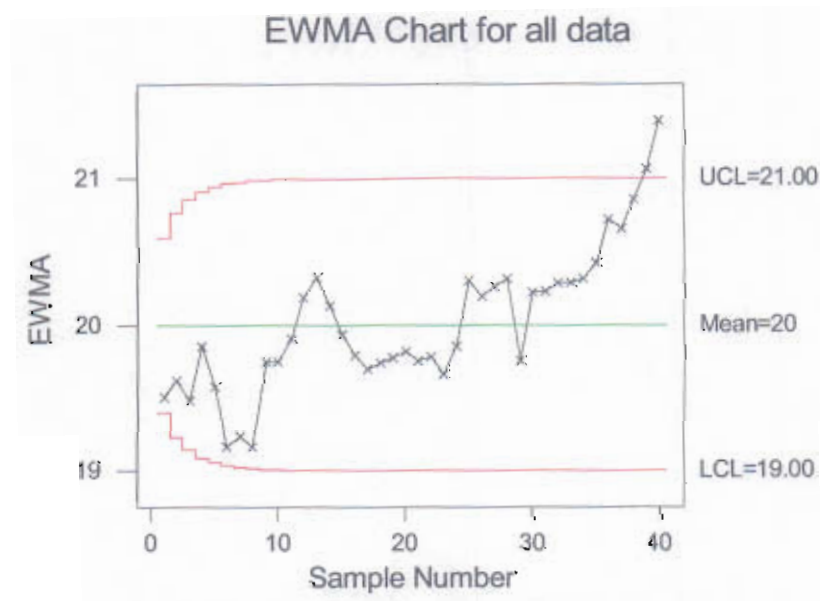
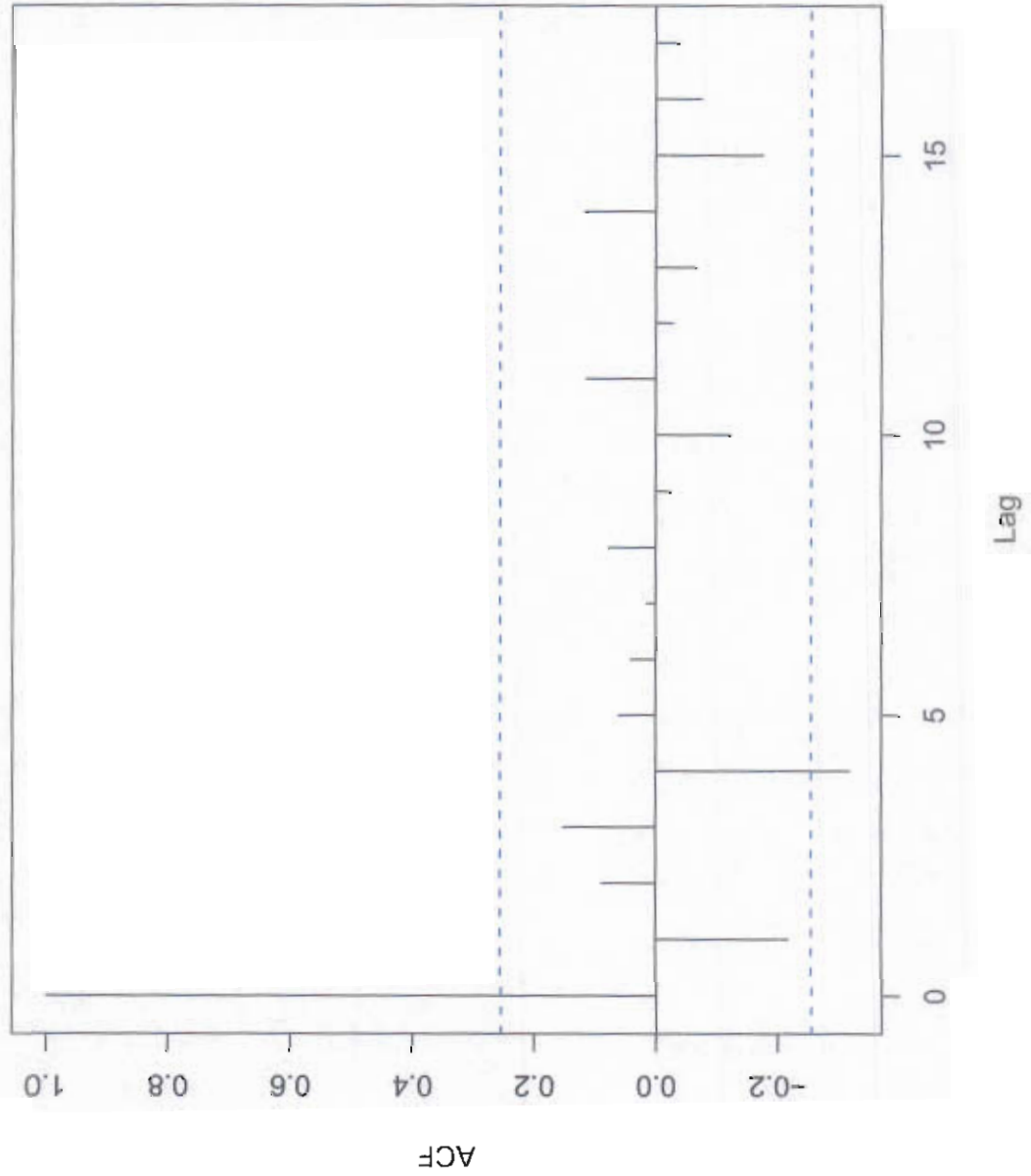


Fig 4

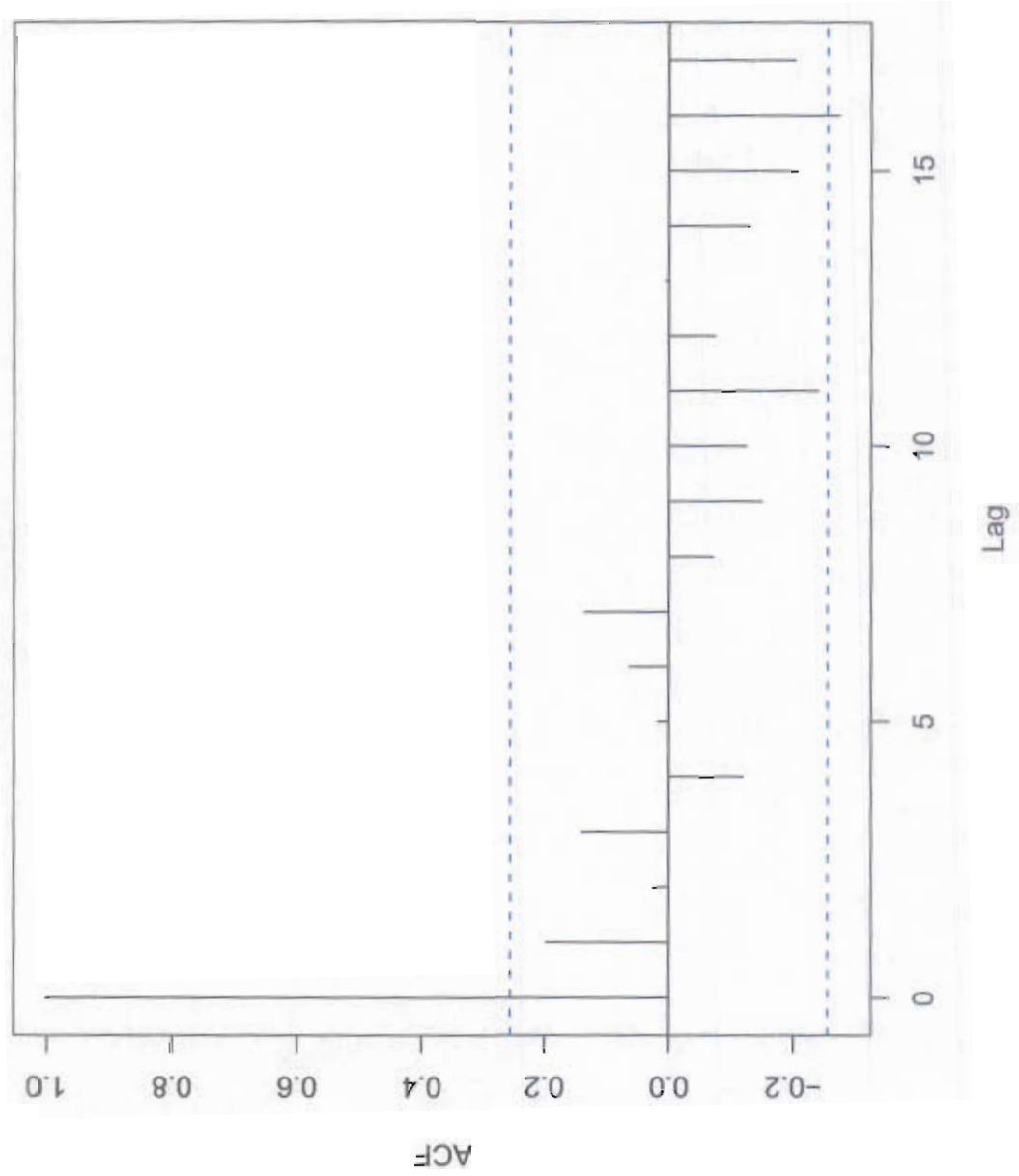


Fleming Motion to Vacate - Appendix A000364

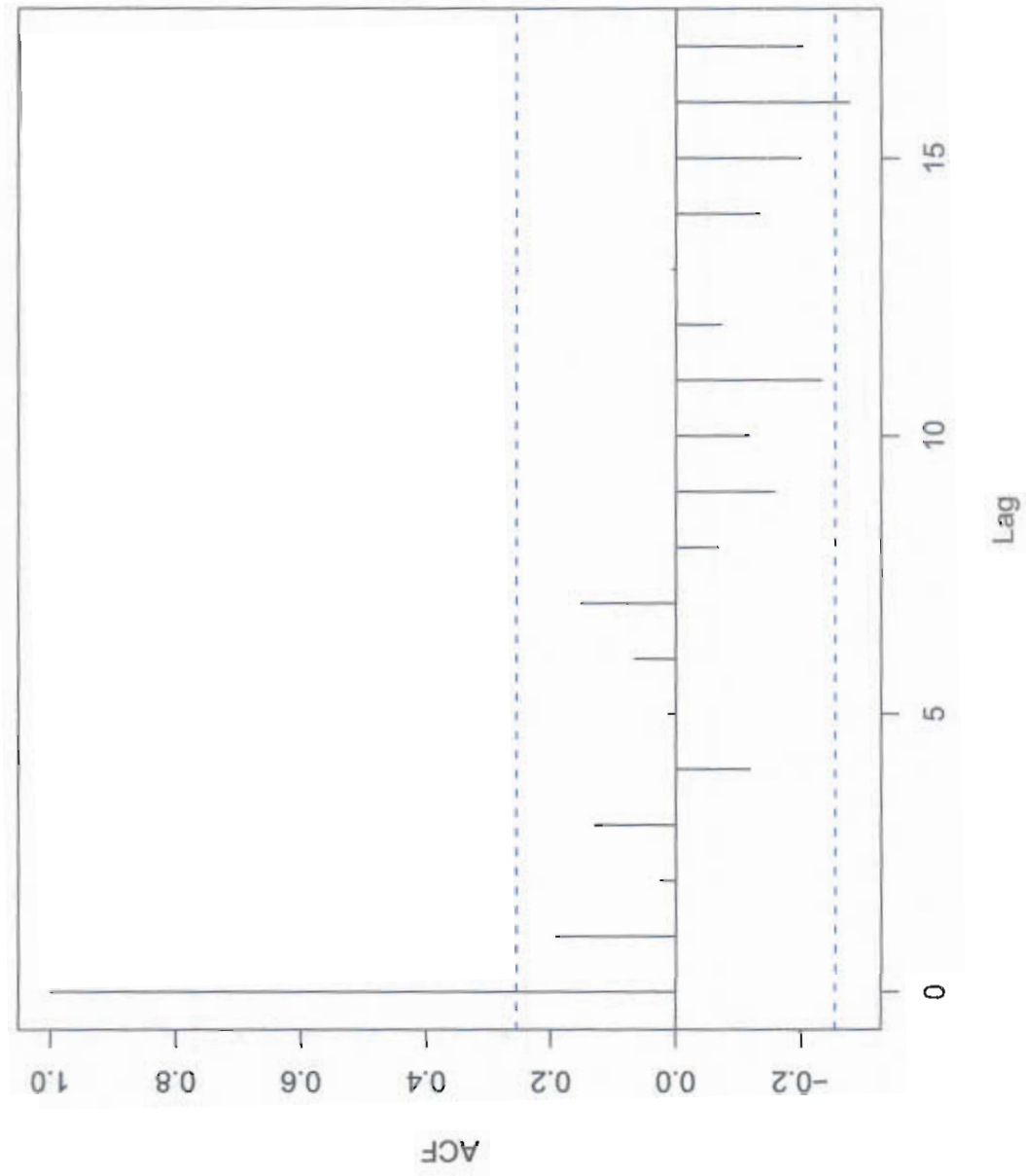
Series rawdata[, "Heights.B"]



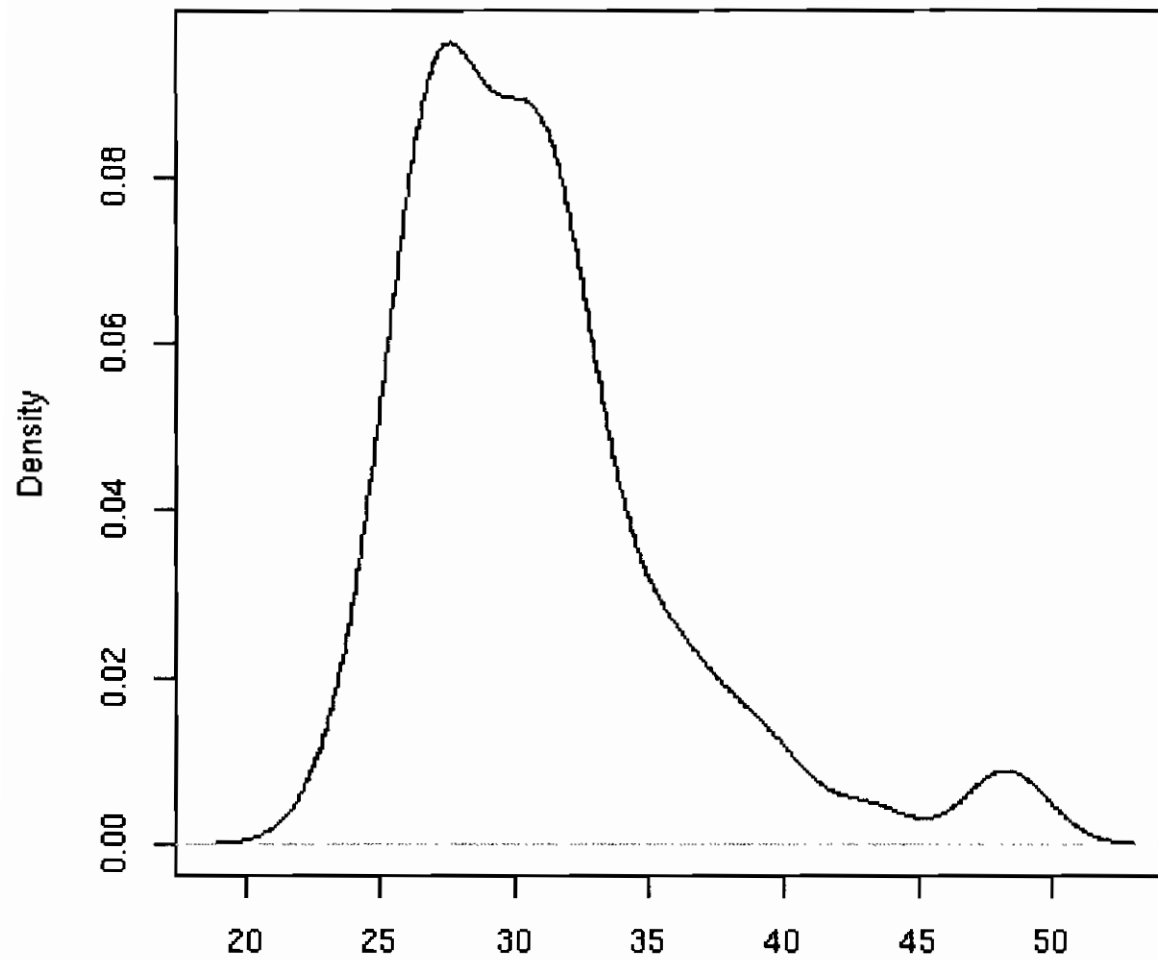
Fleming Motion to Vacate - Appendix A000365
Series rawdata[, "Baseline.Weight"]



Fleming Motion to Vacate - Appendix A000366
Series rawdata[, "X2.Week.Weight"]

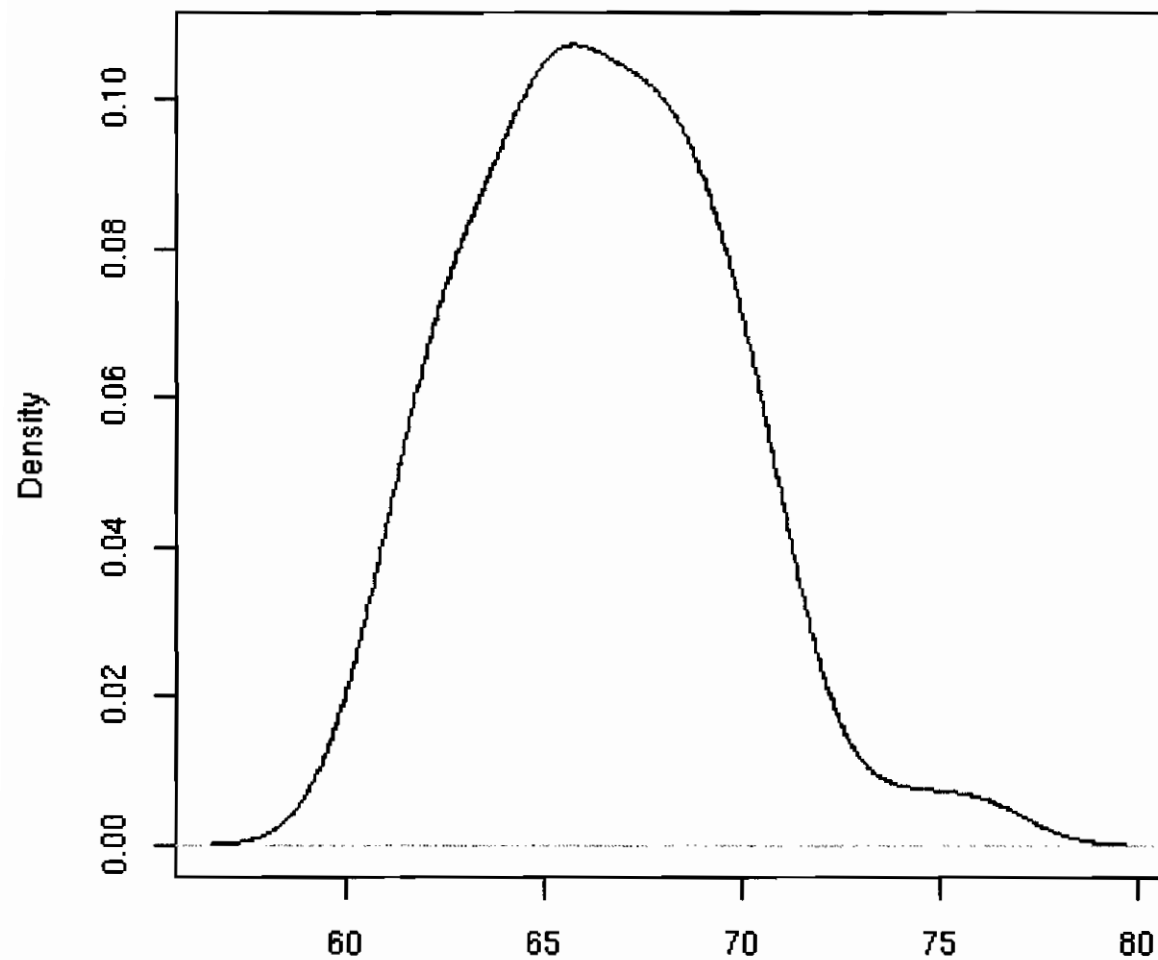


```
density.default(x = rough[["BMI0"]], bw = "nrd0", adjust = 1,  
kernel = "gaussian", n = 512, na.rm = TRUE)
```



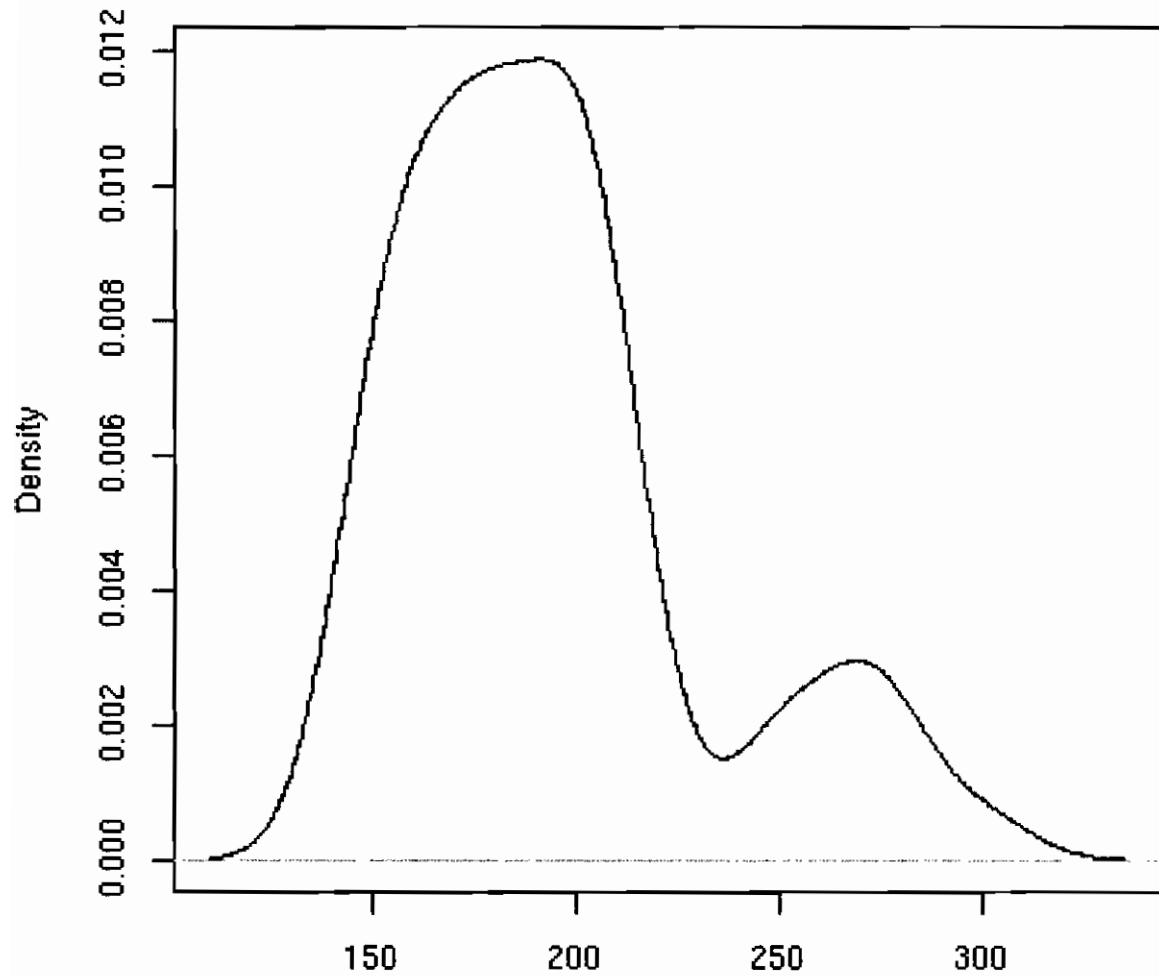
N = 59 Bandwidth = 1.541

```
density.default(x = correcteddata[["Heights.B"]], bw = "nrd0",  
adjust = 1, kernel = "gaussian", n = 512, na.rm = TRUE)
```



N = 59 Bandwidth = 1.289

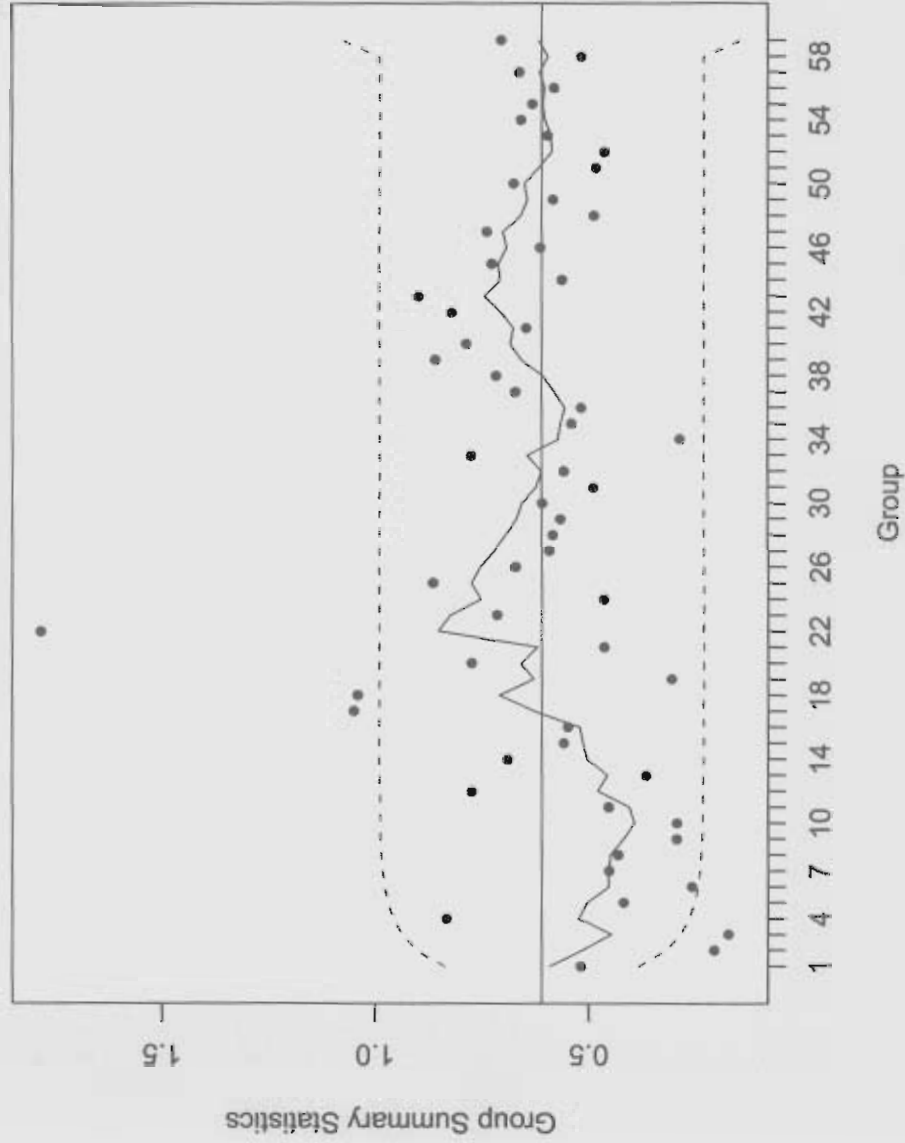
**density.default(x = rawdata[["Baseline.Weight"]], bw = "nrd0",
adjust = 1, kernel = "gaussian", n = 512, na.rm = TRUE)**



N = 59 Bandwidth = 11.81

Fleming Motion to Vacate - Appendix A000370

EWMA Chart for metricdata[, 7:9]

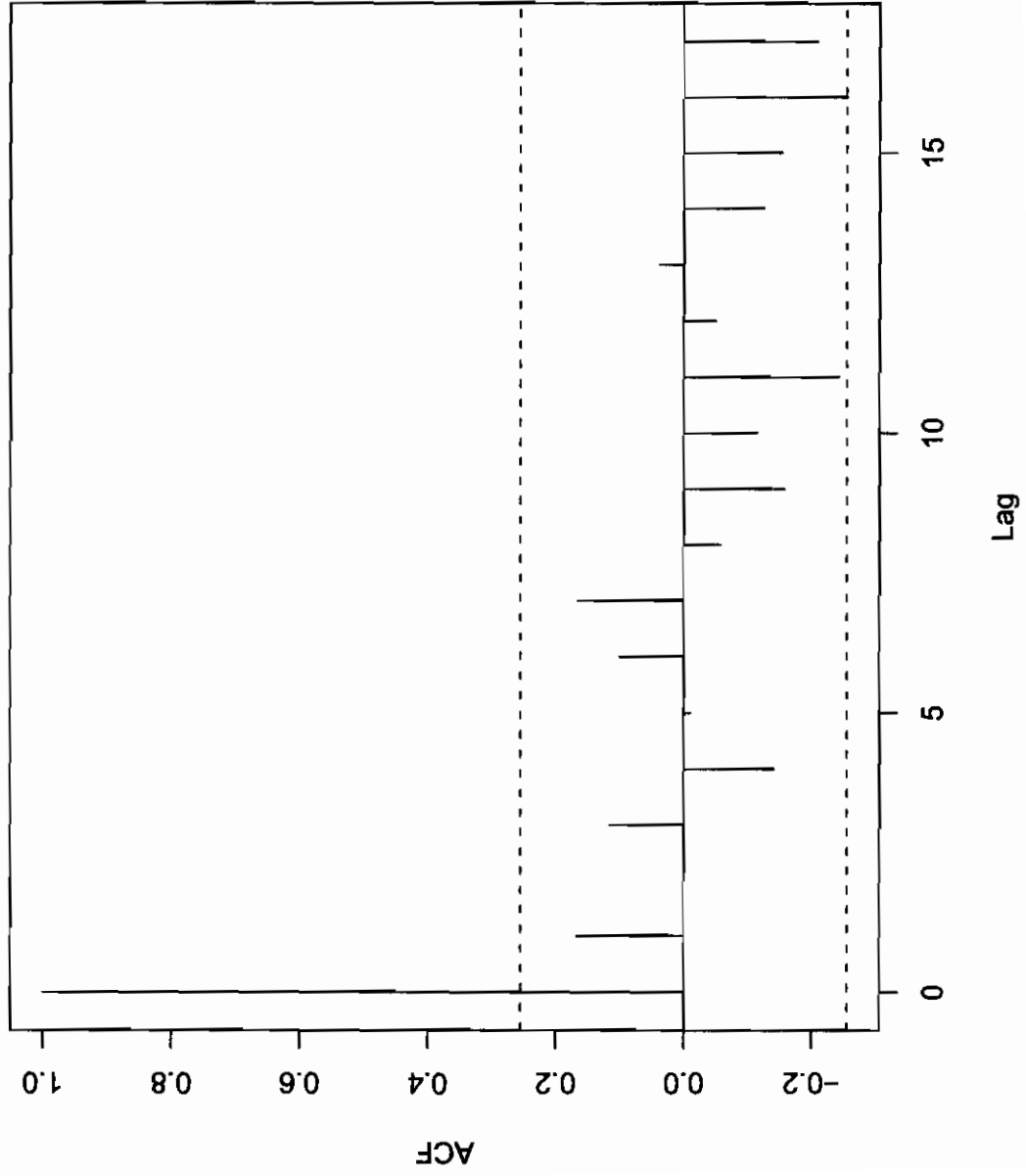


Number of groups = 59
Target = 0.6106348
StdDev = 0.6585494

Smoothing parameter = 0.2
Control limits at 3*sigma

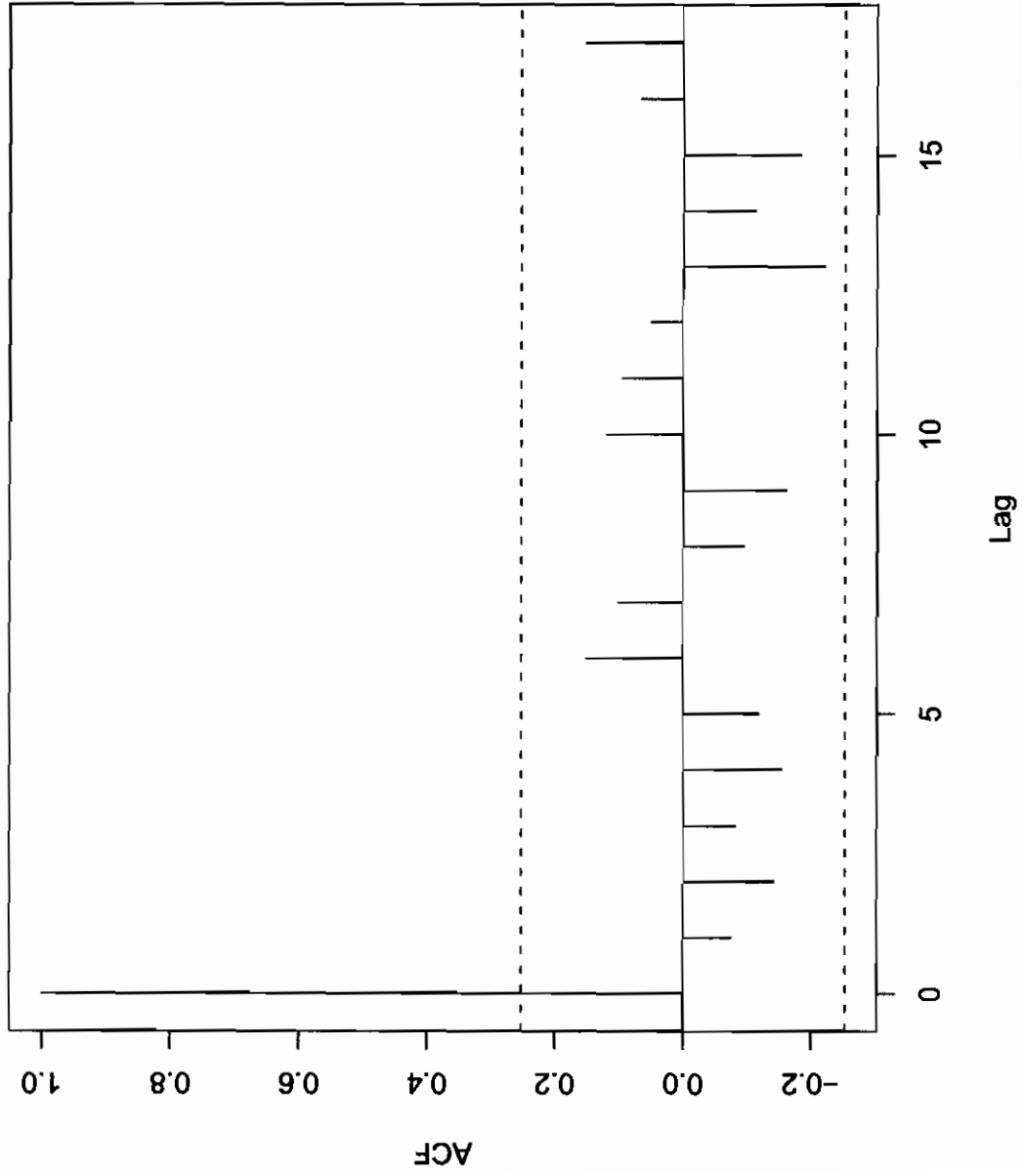
Fleming Motion to Vacate - Appendix A000371

Series rawdata[, "X4.Week.Weight"]



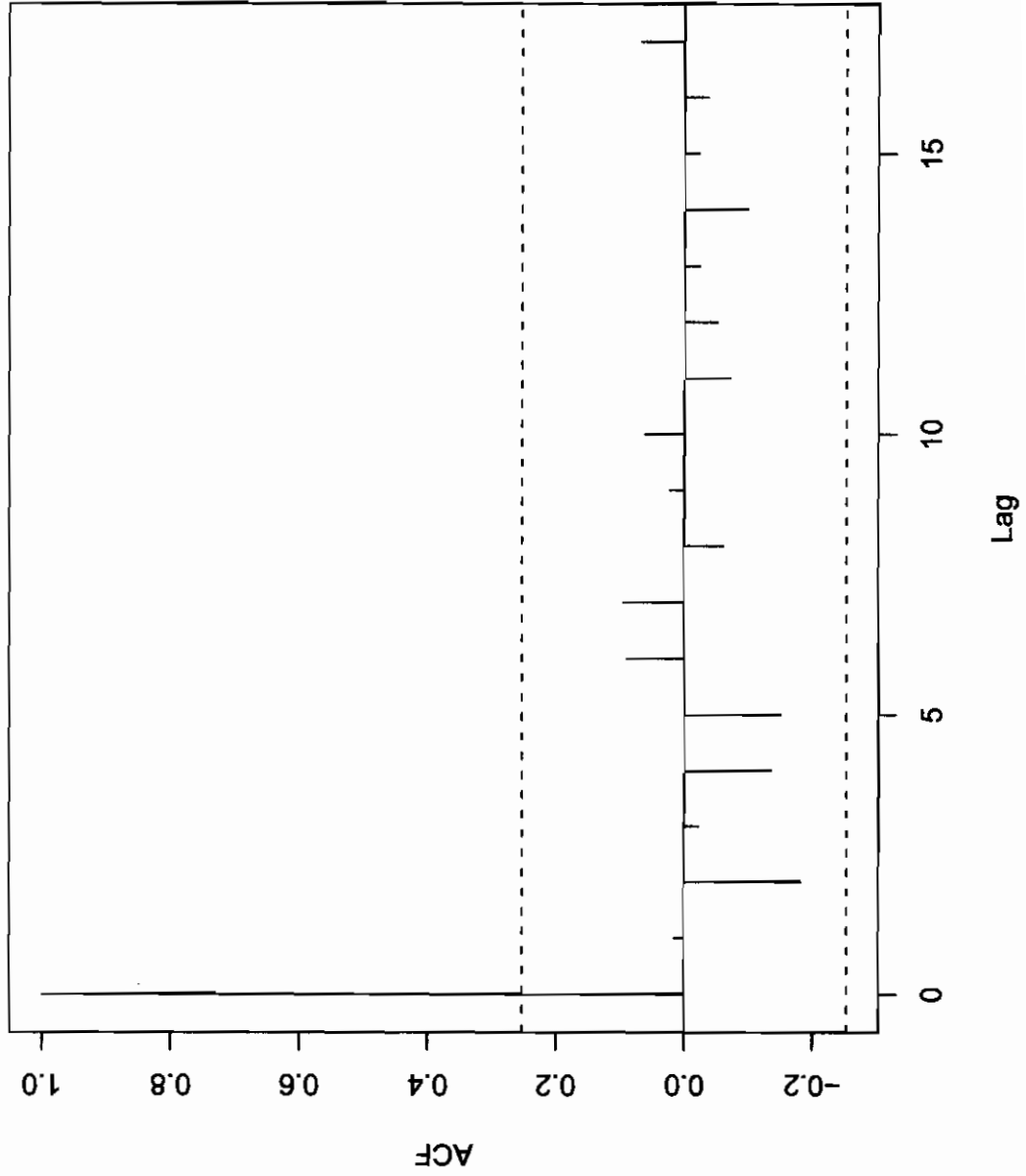
Fleming Motion to Vacate - Appendix A000372

Series fake1[, "Ht"]

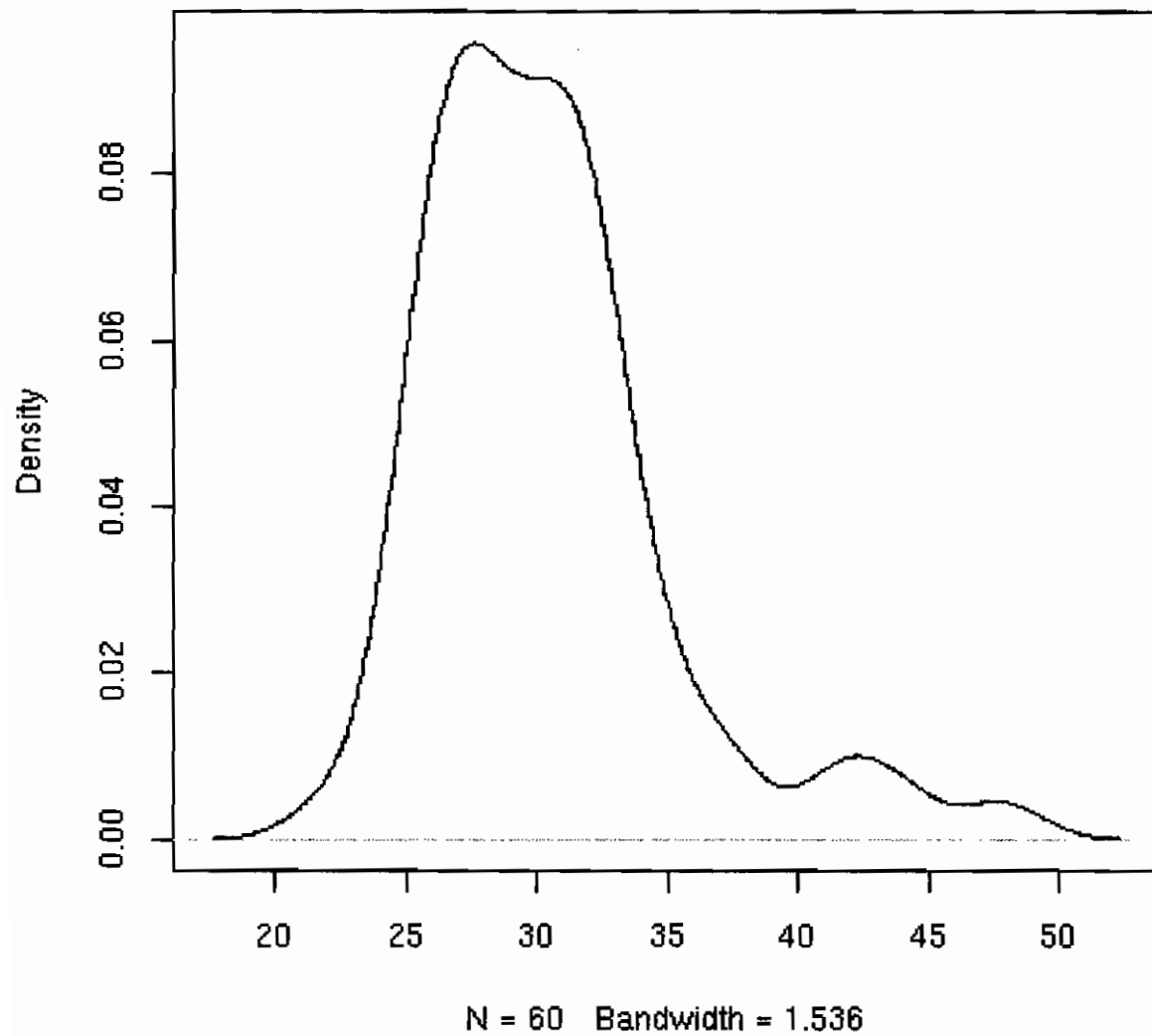


Fleming Motion to Vacate - Appendix A000373

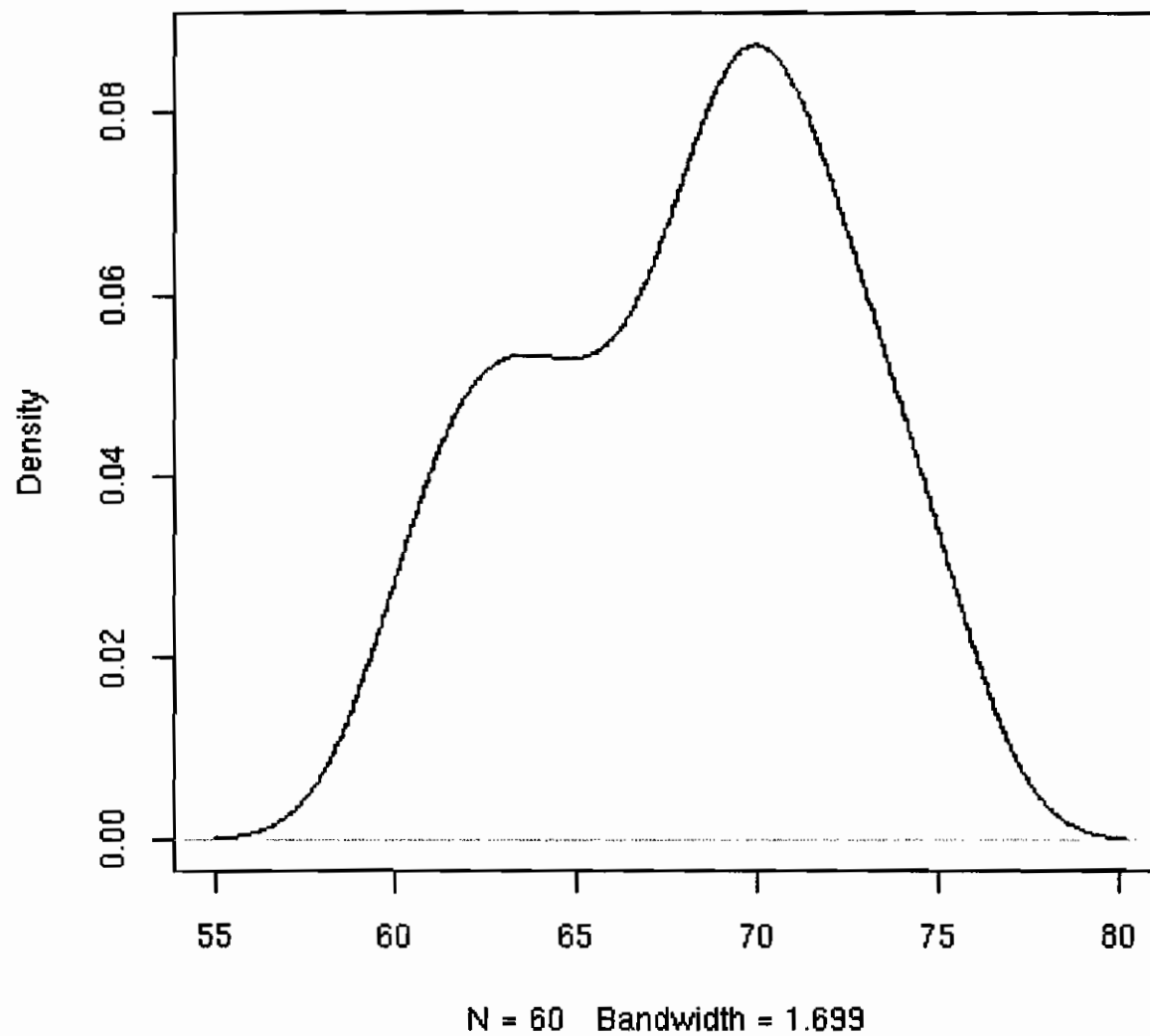
Series fake1[, "Wt0"]

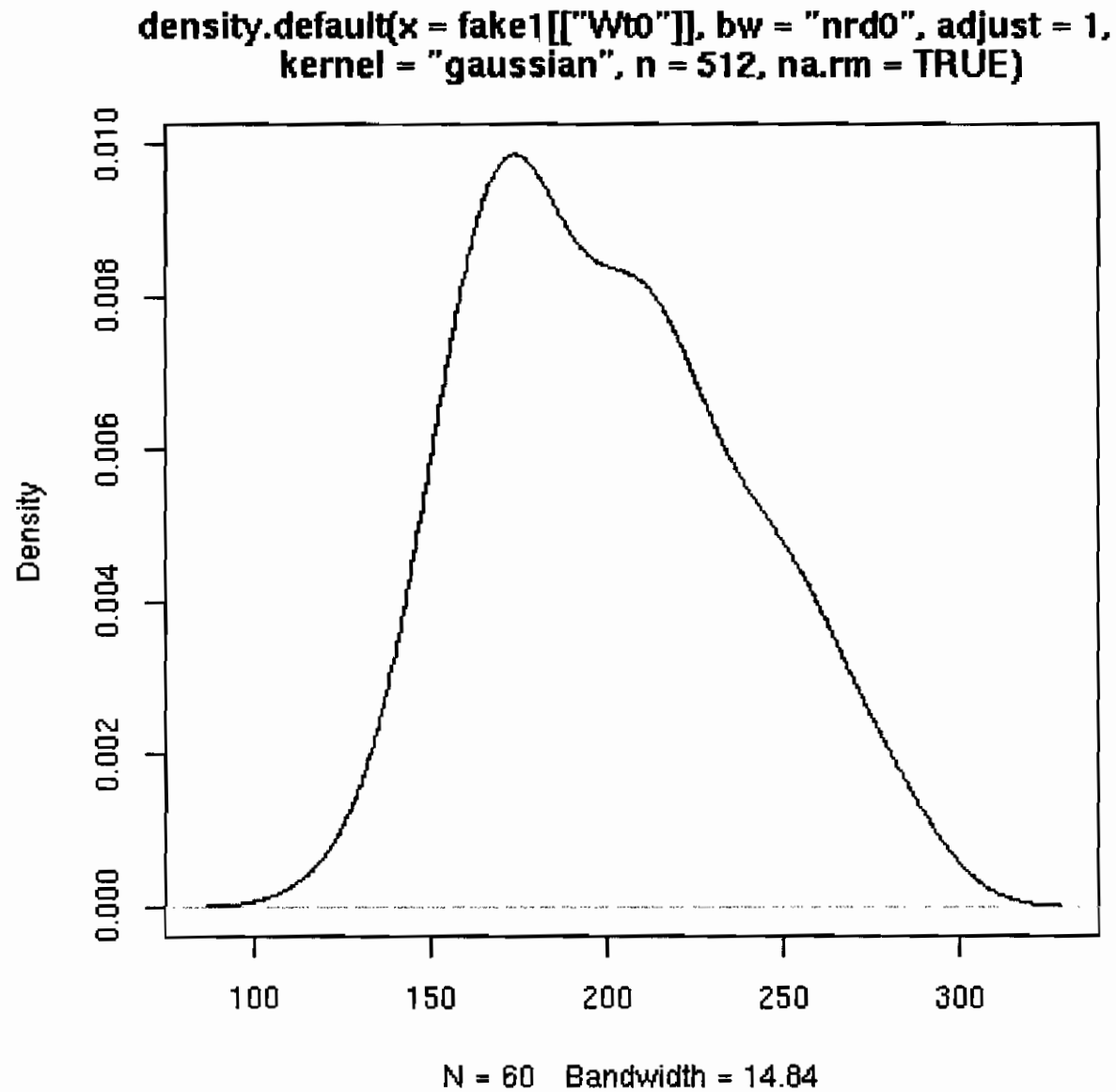


```
density.default(x = fake1[["BMI0"]], bw = "nrd0", adjust = 1,  
kernel = "gaussian", n = 512, na.rm = TRUE)
```



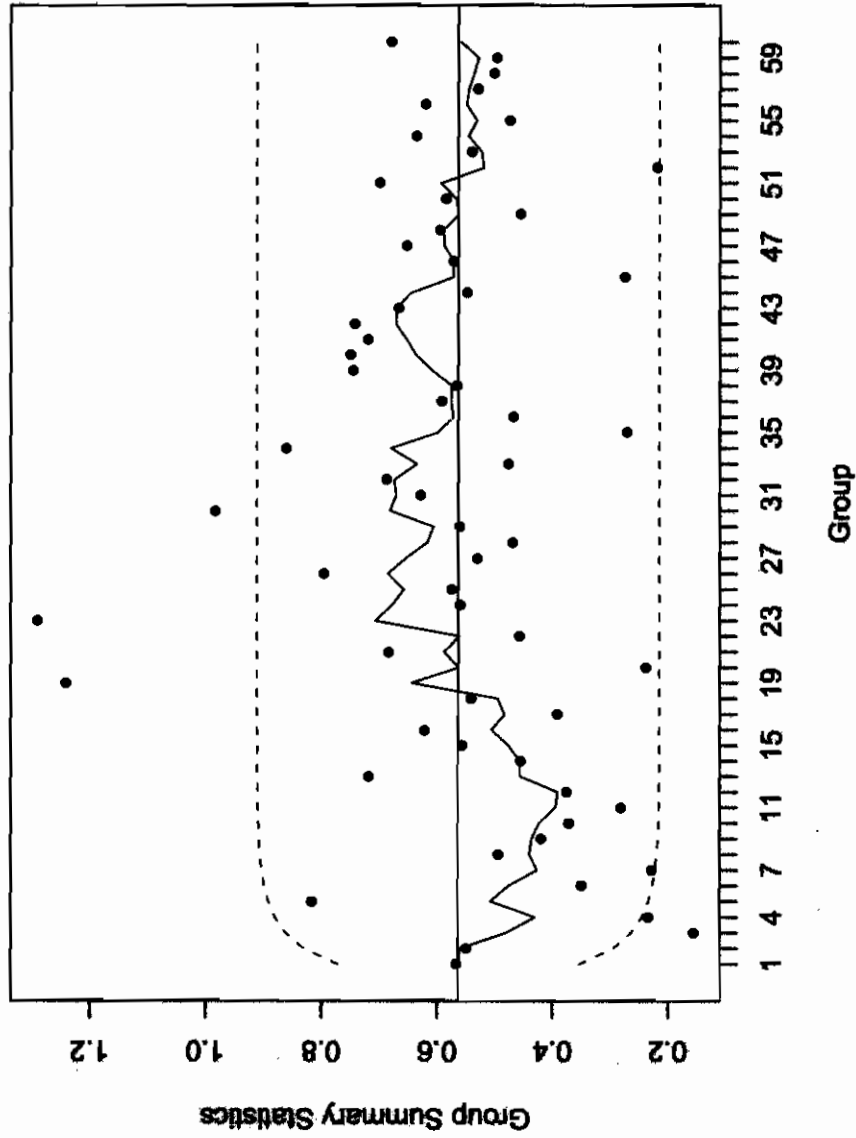

```
ensity.default(x = fake1[["Ht"]], bw = "nrd0", adjust = 1, kernel = "gaus  
n = 512, na.rm = TRUE)
```





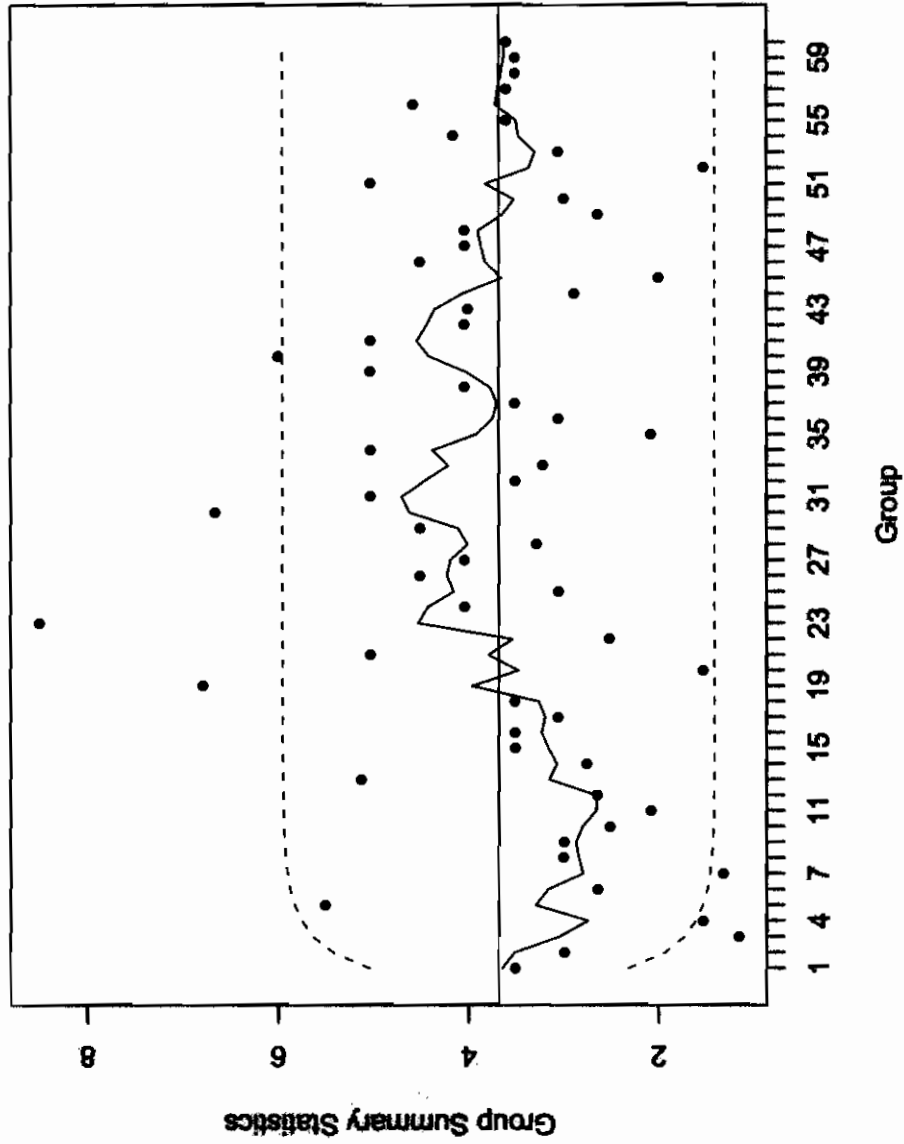
Fleming Motion to Vacate - Appendix A000377

EWMA Chart for fake1[5:7]



Fleming Motion to Vacate - Appendix A000378

EWMA Chart for fake1[, 2:4]

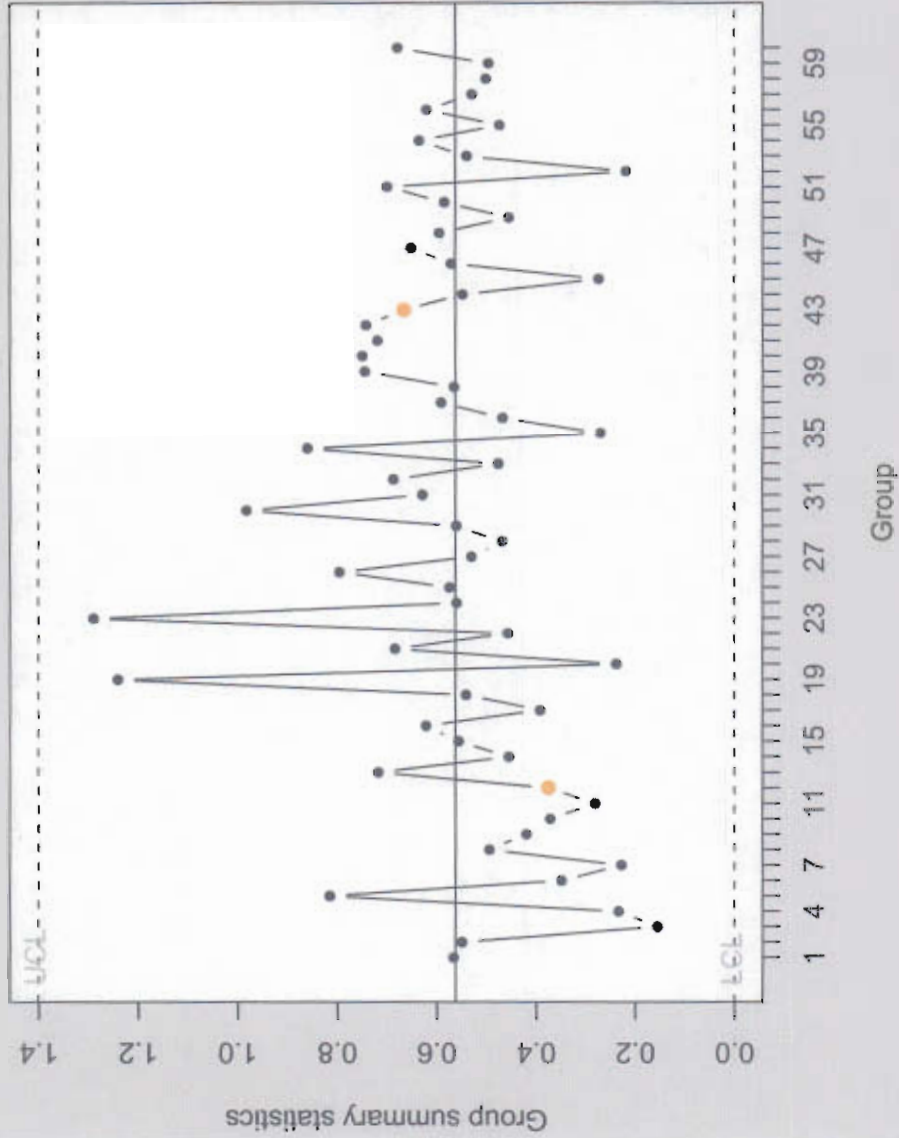


Number of groups = 60
Target = 3.679711
StdDev = 3.935126

Smoothing parameter = 0.2
Control limits at 3*sigma

Fleming Motion to Vacate - Appendix A000379

**S Chart
for fake1[, 5:7]**



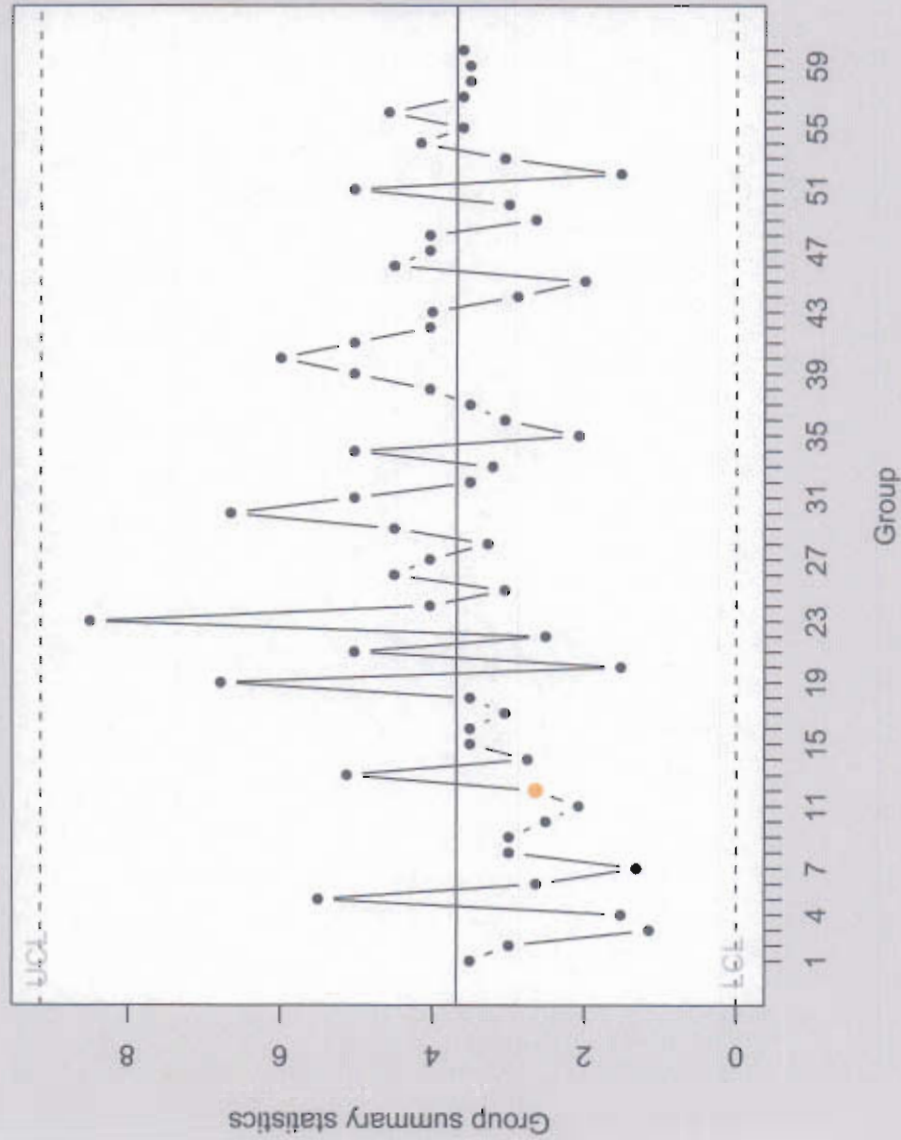
Number of groups = 60
Center = 0.5630041
StdDev = 0.6033196

LCL = 0
UCL = 1.40147

Number beyond limits = 0
Number violating runs = 2

Fleming Motion to Vacate - Appendix A000380

S Chart for fake1[, 2:4]



Re: May 30th

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Fri 4/04/08 6:15 AM

To: RM Fleming (rmfmd7@hotmail.com)

Dr. Fleming,

That May 30 date was set to get the matter off the trial calender. I am still in negotiations with the government and have received no offer from them on the "general proposal" that I discussed with Mr. Everett. That is what my efforts are geared toward at the present moment. After I receive something, I will forward it to you for your review and gear my efforts to determining the viability of your claims on the fraud count.

Thank you, Mike Hansen

RM Fleming
<rmfmd7@hotmail.com>

04/04/2008 07:38
AM

Mike Hansen PD corrected
<mike_hansen@fd.org>

To

cc

Subject

May 30th

Dear Mike,

I hear from the boys that after talking with their mother, I will not be going to prison and that there is a court date for May 30th. PTS in Reno confirms the May 30th date.

Yours,

Dr. Fleming

FW: May 30th

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 4/04/08 1:30 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Thank you Mike.

I hope you have a great weekend and have no doubt that my efforts and those of Dr. Harringtons shows there is no basis for fraud.

Yours,

Dr. Fleming

> Subject: Re: May 30th
> To: rmfmd7@hotmail.com
> From: Mike_Hansen@fd.org
> Date: Fri, 4 Apr 2008 08:17:37 -0500
>
> Dr. Fleming,
> That May 30 date was set to get the matter off the trial calender. I
> am still in negotiations with the government and have received no offer
> from them on the "general proposal" that I discussed with Mr. Everett.
> That is what my efforts are geared toward at the present moment. After I
> receive something, I will forward it to you for your review and gear my
> efforts to determining the viability of your claims on the fraud count.
>
> Thank you, Mike Hansen
>
>
>
> RM Fleming
> <rmfmd7@hotmail.c
> om> To
> Mike Hansen PD corrected
> 04/04/2008 07:38 <mike_hansen@fd.org>
> AM cc
>
> Subject
> May 30th
>
>
>
> Dear Mike,
>
> I hear from the boys that after talking with their mother, I will not be
> going to prison and that there is a court date for May 30th. PTS in Reno
> confirms the May 30th date.
>
> Yours,


>
> Dr. Fleming

Re: Proposed agreements

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Wed 5/14/08 10:40 AM

To: RM Fleming (rmfmd7@hotmail.com)

 2 attachments



RF plea a...pdf (245.8 KB), RF Excl. ...pdf (266.1 KB)

Dr. Fleming,

Please review these documents and we will discuss them Monday, May 19 at 9am in the Hruska Courthouse in Omaha.

(See attached file: RF plea agrmt.pdf) (See attached file: RF Excl. agrmt.pdf)

Thanks, Mike Hansen

THESE TO BE ATTACHED!

RE: missing, follow up

From: **RM Fleming** (rmfmd7@hotmail.com)

Sent: Thu 6/05/08 4:25 PM

To: Mike Hansen (mike_hansen@fd.org)

Bcc: Gordon Harrington (gordon.harrington@uni.edu)

Thank you. I trust you received the information regarding payroll proof of Vicki and Angela's dates of employment.

> Subject: Re: FW: missing, follow up

> To: rmfmd7@hotmail.com

> From: Mike_Hansen@fd.org

> Date: Thu, 5 Jun 2008 10:33:39 -0500

>

> Richard,

> Thank you for the information you have provided on Vicki. We are

> putting it together and prepping to interview her. Attached is the Court's

> Order allowing you to travel to Berlin. Please review it as the Court has

> ordered a couple of conditions of which you must comply. Also, please do

> not tip our hand that as of now, you do not intend to plead guilty in July

> especially to anyone involved in the Court system. That is a matter

> between you and I, and you are unwittingly putting us in a worse position

> by disclosing our timing tactics. Call or email if you have any questions

> or if you cannot access the attachment.

> (See attached file: OK 2 Berlin Order.pdf)

> Mike Hansen

>

>

RE: no contest

From: **RM Fleming** (rmfind7@hotmail.com)
Sent: Thu 5/14/09 4:31 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Thank you.

> Subject: Re: no contest
> To: rmfind7@hotmail.com
> From: Mike_Hansen@fd.org
> Date: Thu, 14 May 2009 11:29:12 -0500
>
> Judge Kopf will not accept a no contest plea.
>
> If you would have waited for the jury to return a verdict, you would have
> been convicted of counts 11, 12, and 13. I believe you would have been
> sent to prison if you would have refused to acknowledge your guilt. Even
> if you finally came around and admitted that you went into the soy chip
> study with the best of intentions, but were unable to get 60 participants,
> panicked and then defrauded Tabor, there is no guarantee that you could
> have avoided prison. Most everyone that goes to trial and loses goes to
> prison. At the time you decided to plead guilty, the deal you made with
> the government was the only real way to avoid going to prison. My
> understanding is that fact was your key motivator in accepting the deal.
>
> I hope this answers your questions.
>
> Mike Hansen
>
>

Fw: Fleming Exclusion

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Wed 5/20/09 6:55 AM

To: rmfmd7@hotmail.com

FYI

----- Forwarded by Mike Hansen/NEF/08/FDO on 05/20/2009 08:55 AM -----

"Palmer, Kathy M
(OIG/OI) "
<Kathy.Palmer@oig
.hhs.gov>

05/20/2009 08:53
AM

"Everett, Alan (USANE) "
<Alan.Everett@usdoj.gov>, "Mike
Hansen" <Mike_Hansen@fd.org>

To

cc

Subject

FW: Fleming Exclusion

Alan and Mike,

Below is information regarding Fleming's exclusion agreement. It apparently went into effect last week - he will be listed on the exclusion database soon. I will ask her about Dr. Fleming getting any paperwork, etc. At the very minimum, I will be sure to send you both a copy of the signed agreement once I receive it.

Thanks,
Kathy

SA Kathy Palmer
USDHHS/OIG/OI
13923 Gold Circle, Suite 215
Omaha, NE 68144

phone: (402) 345-7405
fax: (402) 345-7365
cell: (816) 590-1767
email: kathy.palmer@oig.hhs.gov

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please notify the sender immediately and destroy this e-mail. Any unauthorized copying, disclosure or distribution of the material in this e-mail is strictly forbidden.

From: Mehta, Jaishiri S (OIG/OCIG)
Sent: Wednesday, May 20, 2009 8:45 AM
To: Palmer, Kathy M (OIG/OI)
Subject: RE: Fleming Exclusion

Kathy,

Greg Demske just signed it last week. I will be getting a copy of it today and will forward it to you as soon as I have it. The agreement is effective from the date of the last signatory which was last week. Dr. Fleming's name will appear on the LEIE hopefully within 30-60 days.
Thanks,

Jaishiri

Fw: Fleming Exclusion

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Thu 5/21/09 11:56 AM

To: rmfmd7@hotmail.com



1 attachment



Fleming E...pdf (144.1 KB)

----- Forwarded by Mike Hansen/NEF/08/FDO on 05/21/2009 01:55 PM -----

"Palmer, Kathy M
(OIG/OI) "
<Kathy.Palmer@oig
.hhs.gov>

05/20/2009 11:20
AM

"Everett, Alan (USANE) "
<Alan.Everett@usdoj.gov>, "Mike
Hansen" <Mike_Hansen@fd.org>

To

cc

Subject

FW: Fleming Exclusion

The exclusion agreement was signed on 5/11/09. It is attached. Dr. Fleming will be receiving more detailed information from the office.

Thanks,
Kathy

(See attached file: Fleming Exclusion Agreement 5-11-09.pdf)

Plea Agreement

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Sat 6/20/09 12:54 AM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Cc: rmfmd7@hotmail.com
Bcc: Gordon Harrington (gordon.harrington@uni.edu); Dottie Forsman (dottie@fvrc.net)

 5 attachments



Plea-page...jpg (1435.2 KB), Plea-page...jpg (1252.8 KB), Plea - pa...jpg (1549.6 KB), Plea - pa...jpg (1216.5 KB), Plea - pa...jpg (914.8 KB)

Dear Mike,

I received a correspondence from ASNC earlier today which included a copy of the type written plea agreement document. Before appearing before the Judge, you and I agreeded in writing to one count of medical fraud (viz. I took a static and then dynamic images of the heart and billed 78465 instead of 78464) and one count of mail fraud (viz. the 60 participants did not have written answers, only the bullets filled in). Immediately before the Judge entered the room, Mr. Everett presented the typed Plea Agreement document for us to sign. As I remember, you said it was exactly what was agreed to. However, after receiving the ASNC correspondence today, I had the opportunity to sit down and read it from beginning to end. As a result, there are several things that I do not remember anyone discussing with me and I do not understand. It contains numerous legal references including appeals processes, eg: 28 U.S.C. 2255., 18 U.S.C. 3742, which I do not understand and again do not recall our discussing. I also do not understand what it means when the Judge says anything regarding an agreement to not receive payment from medicare and medicaid (I notice that Mr. Everett included several other items in the document I was instructed to sign, eg. Tricare and "all other Federal health care programs.") is not something he is a part, when it is included under item #2, page 1 of the nature of crime and penalties. What exactly does this mean? Please review the attached written plea agreement document so you know what I have now had the opportunity to read, think about and questions about.

Now that I have had the opportunity to read it, there is a big difference between the plea agreement I wrote out with you and this type written document.

I would also like to know if there is anything else you need from me regarding the financial documents requested by the probation officer whom you have advised me to not communicate with.

Yours,

Dr. Fleming

request

From: **RM Fleming** (rmfmd7@hotmail.com)

Sent: Sat 6/20/09 9:16 PM

To: Mike Hansen PD corrected (mike_hansen@fd.org)

Bcc: Gordon Harrington (gordon.harrington@uni.edu); Dottie Forsman (dottie@fvrc.net)

Dear Mike,

I never did receive a copy of what we wrote and turned into the Judge regarding the plea. Would you please email me a scanned copy.

Thank you,

Dr. Fleming

exclusion

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/03/09 10:53 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

The exclusion deal has a number of items which I do not remember being made aware of including but not limited to the public dissemination of the exclusion. Additionally, BCBS of NE is not a part of the 4th charge which was pled to. This is the first time I have had the opportunity to review (in part) this exclusion. I was never informed what these specific codes are and do not have an understanding of these, including at this time. How can it be claimed that I was not coerced into this agreement when it was part of the requirement by the Prosecution that I needed to sign this for the plea agreement?

Dr. Fleming

emails

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 7/08/09 6:02 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

I wanted to make certain there was no information you needed from me that I have not yet provided. I have sent several emails to you with questions and answers to the plea agreement as you requested. Please let me know the answers to my questions and if there are any answers to your questions I have not responded to or if there is anything I should be aware of that I am not or need to be aware of. As you have said many times, you "are the attorney", so I am depending upon you. The most recent emails with questions and answers include June 16, 19, 20, 26, 29 (10:47 AM and 1:27 PM), and 30th. Also July 1, 2, 3 (12:54 PM, 2:36 PM and 3:53 PM) and the 6th. The times are PST.

Thank you,

Dr. Fleming

Re: further question

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Mon 7/20/09 6:51 AM

To: RM Fleming (rmfmd7@hotmail.com)

Here are the top three:

3. The draft report totally impeached the credibility of Dr. Carriquiry effectively eliminating any possibility of complete acquittal.
2. The draft report showed that anyone could create valid data from a valid representative sample.
- and the number 1 reason why I was upset
1. YOU gave the draft report to the government and they would have never gotten it but for your exceptional arrogance and ignorance.

I hope this clarifies the matter for you.

Mike

From: RM Fleming <rmfmd7@hotmail.com>
To: Mike Hansen PD corrected <mike_hansen@fd.org>
Date: 07/17/2009 04:36 PM
Subject: further question

Dear Mike,

What was the issue and why were you upset that the Judge called you before the bench when he discovered that you had made falsified data using my real soy data?

Dr. Fleming

Jail vs. Plea Deal

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Thu 7/30/09 12:23 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

Why did you tell me that the Judge would send me to Jail if I backed away from the plea deal? Please explain.

Dr. Fleming

> > From: RM Fleming <rmfmd7@hotmail.com>
> >
> > To: Mike Hansen PD corrected <mike_hansen@fd.org>
> >
> > Date: 08/03/2009 01:08 PM
> >
> > Subject: FW: Urgent, please review
> >
> >
> >
> >
> >
> >
> >
> > Mike,
> >
> > As you have instructed me several times, as my attorney, you have
> > directed
> > me not to communicate with the probation office or anyone else on any
> > issues, including finances or other issues, at any time. You have
> > instructed me that you and only you would do that. We have spoken by
> > telephone several times during the last month and you have again directed
> > me to communicate only with you and that you would provide any
> > information
> > required by the probation office or anyone else. You have also told me
> > that violating or rejecting the plea deal would result in the Judge
> > sending
> > me to Jail. In the reports you have attached, it appears to me that there
> > is a question as to the information not being provided to the government
> > and that this would result in a violation of the plea deal. I do not
> > understand! You informed me that you would communicate with them directly
> > providing any and all information required, including but not limited to
> > all the financial information required, which I made available to you
> > before leaving your office after the plea agreement and again since then
> > by
> > telephone. I provided you with all the information they are requesting.
> > Please explain!
> >
> > Dr. Fleming
> >

RE: Urgent, please review

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/03/09 1:09 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I was unaware that the plea agreement included any such provisions. I am confused; because, what I am reading indicates that they received nothing from you and if this violates the plea agreement, this contradicts your instructions to me and your explanation that the Judge would put me in Jail if I violated the plea agreement. I provided you with all this information and filled out the forms for you to supply to the probation office before I left your office in Lincoln immediately after the plea deal. What happened to it? Please provide me with a list of what you need to complete the requested information by the government. WHAT DO YOU NEED-SPECIFICALLY? As you directed me, I will continue not to respond to the probation office; but, leave that in your hands.

Yours,

Dr. Fleming

FW: Urgent, please review

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/03/09 1:20 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

You have copies of my last several years of tax returns, which was required for proof that I required a public defender. I have printed a copy of my bank statement which I will fax to you. What else do you need from me, for you to fill out the forms? What is 18 USC 3664? As already noted and completed on the form before I left your office, I have no stocks, bonds, real estate, promissory notes, or any other monies out there. I have already given you updated vehicle information. I do not own the Hummer. I do not have a spouse. I don't own a business. I have given updated information on monthly expenses. I do expect to obtain custody of Matthew which will increase monthly expenses. I cannot estimate this at this time. I made the plea agreement in order to be able to care for him. Do you need anything else from me?

Dr. Fleming

voice mail

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/03/09 4:02 PM
To: **Mike Hansen PD corrected** (mike_hansen@fd.org)
Bcc: **Gordon Harrington** (gordon.harrington@uni.edu)
Mike,

This is to confirm your voice mail today explaining that you have hard copies of the documents in question; but, that you want them from me in one package. That you are too busy to find the documents and that if I do not have them to you within 48 hours the Judge will hold me in contempt of court, throw out the plea deal and send me to prison.

Dr. Fleming

documents

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 8/04/09 12:15 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)



1 attachment



3 August ...doc (21.4 KB)

Mike,

I have sent to you by Express Mail, the documents you requested. It should reach you by noon tomorrow (8-5-2009) and will require a signature. I made the Plea Deal to avoid going to Jail, so I could raise Matthew. I would like to know from you what would happen if I withdraw the plea deal?

Yours,

Dr. Fleming

plea

From: **RM Fleming** (rmfmd7@hotmail.com)

Sent: Tue 8/04/09 12:35 PM

To: Mike Hansen PD corrected (mike_hansen@fd.org)

Bcc: Gordon Harrington (gordon.harrington@uni.edu); Fred Atcheson (fatcheson@fedcrim.com); Fred Atcheson (fatcheson@fedcrim.com)

Mike,

How do I withdraw the plea, if I think there is good reason for doing so?

What would be the consequences?

Dr. Fleming

plea vs. guilt

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 8/04/09 4:16 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

It is my understanding following our discussion today, that the Judge would send me to jail even after withdrawing the plea deal, since the Judge would still consider me guilty independent of any proof of innocence. I only pleaded guilty so I could remain out of Jail and raise my son. The agreement to never bill medicare and medicaid again seems excessive to me and now includes a number of other items which was not discussed. You have assured me; however, that only by signing this document would the prosecutor agree to recommend that I not go to Jail.

Please let me know if you have any questions or need any further information after you received the documents tomorrow.

Yours,

Dr. Fleming

FW: plea vs. guilt

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 8/04/09 4:51 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

Thank you also for confirming today that the Judge would not let me withdraw my plea of guilty even with proof of innocence.

Yours,

Dr. Fleming

Response from Matthew. This is the second and final version from him.

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 8/05/09 5:33 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Matthew had an additional item he wanted to make!!!!

See # 11 below.

From: rmfmd7@hotmail.com
To: dchristensen@mcrlawyers.com
Subject: RE: my license
Date: Wed, 5 Aug 2009 16:49:59 -0700

Dave,

Here are Matthew's reasons (from him):

- 1) I feel a lot more protected here with my dad, With my mom I never know if she is going to be upset or just be angry for no reason at all and take it out on me.
- 2) I am told the truth when ever I am at my dad's, When I am with my mom I can almost always tell that she is lying to my face and she thinks I am believing it.
- 3) She has abused me and been told by police officers that she will be charged with child abuse.
- 4) She tells me things like my dad will abduct me and every single time that I have seen my dad he has never abducted me and has always sent me back because he has to but I would like to stay.
- 5) When ever I mention dads name then she always makes bad remarks about him trying to get me to believe that he is the worst person in the world.
- 6) I have also heard her talking on the phone with the F.B.I. and she has been talking to them about trying to find a way to put my dad in jail and they have also told her where my dad is at all times since the divorce.
- 7) She has said that I would have a great life in Wisconsin and tries to make me feel bad about leaving like saying that the only reason that she wanted to live in Wisconsin is because she wanted to be able to take care of me with money from a job that I don't even know of. But she makes comments to me of "go live with your dad" then she will say "oh thats right the judge won't allow you to live with an unstable parent.
- 8) She says that I will love Wisconsin. I don't care about what places are around me or what state I am living in, I care about the parent I am living with. I WANT TO LIVE WITH MY DAD!!!
- 9) She has made fun of all of us (Stephanie, Christian, and Me) behind our backs. She has talked to her friends and all she says is that she wishes that she could replace us with our cousins or even our friends and even calls us brats behind our backs. She makes remarks that anything that we do wrong is either my dad's falt or it is just in the jeans that we got from our dad.
- 10) Recently my brother and I got into a fight and I ended up bleeding. When I was looking for help I could not reach my mom on the phone at all. So I had called my dad and immediatley he had answered and he had told me to call the police and the paramedics and when my mom had finally been reached and made it to the emergency room then she was more concerned about the money that would have to be payed to cover the ambulance and the cat scan to see if anything was broken. Also the last time I ever took any money out of my account at the bank there was a little over seven hundred dollars in my account and just recently she has told me that there was only two hundred dollars in my account. So I am thinking that my mom has taken money out of my bank account to pay for the ambulance ride.
- 11) I hope that the Judge favors my side but I am a little concerned because my mom keeps making bad comments about the Judge like that he is unfit for the job. Thank you!

Sincerely,

Matthew Ryan Fleming

> Date: Wed, 5 Aug 2009 15:35:06 -0500
> From: DChristensen@mcrlawyers.com
> To: rmfmd7@hotmail.com
> Subject: Re: my license
>
> I emailed the docboard for a copy of the license. Will that work? Can you have Matthew list some reasons why he does not want to go back before the trial and I will put it in affidavit form for him to file and I will see if the Judge will look at this in an emergency situation and order that he can extend his vacation with you until the 19th.
>
> David A. Christensen
> Marks Clare & Richards, L.L.C.
> 11605 Miracle Hills Drive, Ste 300
> Omaha, NE 68154-8005
> (402) 492-1783 (Direct Dial)
> (402) 492-9800
> (402) 492-9336 (Fax)
>

FW: Richard Fleming Sentencing Recommendation

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 8/14/09 3:08 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)



1 attachment



FLEMING,R...pdf (29.4 KB)

Mike,

I don't understand what is actually being said. It sounded like they are sending me to jail. Is that what they are doing?

Dr. Fleming

Re: soy and AVON & Revival soy

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Wed 5/14/08 1:07 PM

To: RM Fleming (rmfmd7@hotmail.com)

Dr. Fleming,

What I would like you to think about between now and Monday is this, despite the fact that you believe Vicki's independent recollections violate HIPAA when questioned by OIG (they do not), she and others will be allowed to present their perceptions of whether it is even a remote possibility that there were 60 participants in the soy study. Without your testimony to the contrary (which as we discussed and will discuss is severely problematic), all the statistics in the world will not significantly alter the picture the government will present to 12 members of the general public that you signed your name to a materially fraudulent study.

In other jury trials I have done, Judge Kopf has quoted Mark Twain to the jury: "There are lies, there are damn lies, and then there are statistics." The government's case in chief on the mail fraud count is not complicated. Its impeachment of you, should you choose to testify, will be, and I promise you they have not given me everything they have to shed doubt on your veracity. I have set aside my entire Monday to discuss these matters with you. If you believe we may need to review all the evidence and our materials, it might be easier to have the meeting in my office in Lincoln. Otherwise, I will bring everything related to the soy study and we will review it together in Omaha.

Thanks, Mike Hansen

FW: no contest

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Thu 5/14/09 4:30 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I have not yet been contacted by anyone from Probation; although, I note my credit score has been marked by the probation office asking about my credit. In addition to the two questions below, do you know or have you heard from anyone, as to why the two cases of FH Washout on the ASNC website have been withdrawn? I certainly didn't do it and it is bothersome to think that the "Justice" system would now be practicing "Medicine". Since I have no idea, I am simply asking if you have heard anything.

Dr. Fleming

To: mike_hansen@fd.org
Subject: no contest
Date: Wed, 13 May 2009 15:49:42 -0700

Dear Mike,

Am I correct that you told me that Judge Kopf does not accept no contest pleas?

I also understood that if guilty on counts 11-13, that there would definitely have been jail time without a plea deal. Is that also correct?

Dr. Fleming

letter

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 6/03/09 11:53 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I have received the letter dated June 1, 2009. I am unclear what is so "unusually complex" and I do not know what paragraphs 3 through 9 of the sentencing schedule means.

Please clarify.

Thank you,

Dr. Fleming

Stanley

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Sun 6/14/09 12:35 AM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

I have received a packet from Mr. Stanley L. Pfeiffer (Senior U.S. Probation Officer) regarding financial statements to be provided to him by Monday, June 22, 2009. Along with a request to call him should I have any questions. Since you instructed me to notify you should he contact me and since you specifically instructed him not to contact me, I am letting you know I have received said packet and would like further instructions from you as to what should be done.

Dr. Fleming

probation officer

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 6/16/09 4:31 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)

Dear Mike,

I called yesterday and left a message (in addition to the email this weekend) regarding the probation officer sending me material to be sent to him. What are you instructing me to do, if anything, with this material.

Yours,

Dr. Fleming

good morning

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 6/26/09 4:02 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington - Private (dryfly@fvrc.net)
Dear Mike,

I am working on a number of projects today.

I received your email yesterday from the probation office and have "briefly" reviewed it.

- 1) The medicare fraud is a single count. I did not plead guilty to 72 other counts of medicare fraud and they were not introduced in court.
- 2) From a mail fraud count, the money paid by Tabor was \$25,000 and I am unclear as to what part of this is to be paid back. How can they determine which part of \$25K is owed.
- 3) I did not interfere with an Investigation in any way. I did what Calkins told me to do (and he was there to say something if I was interfering) and what you told me to do.
- 4) I don't have \$9,000 in cash. I do have \$9,000 charged on my credit card.

I will try to get more done this weekend and get back to you Monday or Tuesday depending upon what works for us.

Yours,

Dr. Fleming

restitution

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 6/29/09 8:27 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

Please explain to me what is going on and the legal procedures that allow the probation officer (Pfeiffer) to contact a former patient of mine whose name was not mentioned in the trial and ask him to fill out a form for restitution and giving the date, time and place of sentencing.

I have never heard of anything like this. According to this individual the court is going to determine restitution and who gets it. None of this is within the plea discussions and I have not pled to anything else.

I find nothing appropriate about this.

Dr. Fleming

exclusion agreement

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 7/01/09 5:44 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

Why did I have to sign an exclusion agreement since the law already provided for exclusion?

Dr. Fleming

FW: exclusion agreement

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Thu 7/02/09 4:26 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I also notice that the exclusion keeps me from working for anyone (eg. a hospital) which bills medicare or medicaid. I wasn't aware that this was to be an exclusion. How is it possible that the government is worried about the hospital overbilling when they (not I) would make the determination from their coders? This exclusion, as mentioned previously, had a number of things placed in it that wasn't agreed to. Why wasn't this caught? Did Everett mentioned these things to you?

Dr. Fleming

additional questions

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/03/09 7:54 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

What is the legal significance and use of the Probation Office pre-sentencing report? I have submitted responses to the items in the report as you requested me to and have not heard back from you and I still do not understand the implications of what is being done. Please explain!

Dr. Fleming

ASNC

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/03/09 9:36 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

Why has the American Society of Nuclear Cardiology received a copy of my plea agreement?

Why has the Iowa Medical Board received notification of my being convicted of felonies amongst other things?

Dr. Fleming

exclusion

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/03/09 10:53 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

The exclusion deal has a number of items which I do not remember being made aware of including but not limited to the public dissemination of the exclusion. Additionally, BCBS of NE is not a part of the 4th charge which was pled to. This is the first time I have had the opportunity to review (in part) this exclusion. I was never informed what these specific codes are and do not have an understanding of these, including at this time. How can it be claimed that I was not coerced into this agreement when it was part of the requirement by the Prosecution that I needed to sign this for the plea agreement?

Dr. Fleming

credibility

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 7/06/09 9:14 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

Why didn't anyone question the validity of what Vicki or Angela said?

Dr. Fleming

exclusion

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/03/09 10:53 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

The exclusion deal has a number of items which I do not remember being made aware of including but not limited to the public dissemination of the exclusion. Additionally, BCBS of NE is not a part of the 4th charge which was pled to. This is the first time I have had the opportunity to review (in part) this exclusion. I was never informed what these specific codes are and do not have an understanding of these, including at this time. How can it be claimed that I was not coerced into this agreement when it was part of the requirement by the Prosecution that I needed to sign this for the plea agreement?

Dr. Fleming

emails

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 7/08/09 6:02 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

I wanted to make certain there was no information you needed from me that I have not yet provided. I have sent several emails to you with questions and answers to the plea agreement as you requested. Please let me know the answers to my questions and if there are any answers to your questions I have not responded to or if there is anything I should be aware of that I am not or need to be aware of. As you have said many times, you "are the attorney", so I am depending upon you. The most recent emails with questions and answers include June 16, 19, 20, 26, 29 (10:47 AM and 1:27 PM), and 30th. Also July 1, 2, 3 (12:54 PM, 2:36 PM and 3:53 PM) and the 6th. The times are PST.

Thank you,

Dr. Fleming

FW: emails

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/10/09 5:58 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

I believe a response was required by the 13th of July for the probation report. As noted with my prior emails, I have responded to this and other issues as best I can. Please let me know what your response is to the probation report and my other questions and what if any questions you need me to answer or information you need from me.

Yours,

Dr. Fleming

Do you have any questions?

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 7/13/09 5:04 PM
To: Mike Hansen PD corrected (mikc_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

I haven't heard anything from you in weeks and have received no answers to my questions or responses from you regarding my responses to the probation report or the plea agreement. Please let me know if there is anything else you need to move forward. Since I originally encouraged you to find the original soy data sheets, where they ever found?

Yours,

Dr. Fleming

RE: Do you have any questions?

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 7/13/09 8:35 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I did not receive the telephone call from you as promised. Is the presentence report the probation officers report?

Dr. Fleming

FW: guilt by association

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/17/09 2:34 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)



1 attachment



RPSR.pdf (121.6 KB)

Dear Mike,

Is the new report any different from the prior report? If so, how? If so, how does it answer any of my questions posed to you previously?

Yours,

Dr. Fleming

guilt by association

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/17/09 9:01 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

I have a potential VA position offered to me. Why should the exclusion for medicare and medicaid interfere with my employment if the argument is that I improperly billed 78465 instead of 78464? Does the government conclude that anyone associated with me will automatically bill incorrectly? If not, then why was the exclusion document worded to prevent me from working with others determining what should be billed? In addition, why should the plea agreement prevent the current Judge from hearing an appeal?

Dr. Fleming

further question

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/17/09 9:38 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Dear Mike,

What was the issue and why were you upset that the Judge called you before the bench when he discovered that you had made falsified data using my real soy data?

Dr. Fleming

RE: guilt by association

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/17/09 10:07 PM
To: **Mike Hansen PD corrected** (mike_hansen@fd.org)
Bcc: **Gordon Harrington** (gordon.harrington@uni.edu)
Mike,

Specifically, this was not a medical malpractice case. The probation officer is now rendering his opinion as to whether (bottom of page 2 of the addendum) his statement: "there was no medical value". This is not what the evidence proved nor what the case was about. Under page 3 of the addendum, he fails to understand the \$25,000 paid for the soy chip study and that of any other study. Page 3 of probation officers report talks about rest versus stress. In all of the evidence submitted, the protocol clearly showed the sequence of what was done and their witnesses as well as ours, shows the sequence independent of what an image is called. Therefore, there is no obstruction of justice.

What other thoughts do you have to this or my questions below?

Dr. Fleming

Re: further question

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Mon 7/20/09 6:51 AM

To: **RM Fleming** (rmfmd7@hotmail.com)

Here are the top three:

3. The draft report totally impeached the credibility of Dr. Carriquiry effectively eliminating any possibility of complete acquittal.
2. The draft report showed that anyone could create valid data from a valid representative sample.
and the number 1 reason why I was upset
1. YOU gave the draft report to the government and they would have never gotten it but for your exceptional arrogance and ignorance.

I hope this clarifies the matter for you.

Mike

From: RM Fleming <rmfmd7@hotmail.com>
To: Mike Hansen PD corrected <mike_hansen@fd.org>
Date: 07/17/2009 04:36 PM
Subject: further question

Dear Mike,

What was the issue and why were you upset that the Judge called you before the bench when he discovered that you had made falsified data using my real soy data?

Dr. Fleming

RE: further question

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 7/20/09 3:35 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Mike,

I still don't understand what you did to fake your data from my real data and why the Judge was upset with you and what he was talking about when he said he wasn't going to let you become a witness nor withdraw from the case. How did you fake the data and why would you have had to withdraw from the case as my attorney?

Dr. Fleming

RE: Fleming Loss and Restitution Information

From: RM Fleming (rmfmd7@hotmail.com)
Sent: Wed 7/22/09 2:30 AM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington - Private (dryfly@fvrc.net)
Mike,

I am also objecting to information being used which has never been proven in court.

Dr. Fleming

FW: Fleming Loss and Restitution Information

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 7/22/09 3:58 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)



2 attachments



072009 Re...xls (32.3 KB), 060409 Fl...doc (39.4 KB)

Mike,

Why is Kathy Palmer generating a report when the probation officer already has? Why is the Public Defender and Kathy Palmer trying to prove medical malpractice and why was this permitted at trial when the trial was not about medical practice? Not only did the Judge point out to the Jury that this was not about medical practice; but, he also pointed out that taking images at 5 and 60 minutes post stress was medically useful in at least one instance as testified by Dr. Jay!

Diane and Palmer

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 7/22/09 5:59 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu); Gordon Harrington - Private (dryfly@fvrc.net)
Mike,

How did you know that Kathy Palmer and Diane had been talking when I was called before the Magistrate Judge after traveling 8 miles into Nebraska from Iowa to pick up the boys for the weekend as ordered by the Divorce Judge?

Dr. Fleming

response

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 7/24/09 10:56 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

The prosecution is attempting through the pre-sentencing report to get a conviction on a charge that which was never brought in court, heard in court and to which I did not plea. How do we handle that?

Dr. Fleming

response to you

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Sat 7/25/09 12:49 AM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I have reviewed the CD titled "Payment records"

- 1) Checks do not constitute evidence of medical practice.
- 2) This information has never been seen by myself before and to the best of my knowledge, you have not either.
- 3) The legality of how this information was obtained without a legal order by the court to do so raises questions which I think need to be addressed as to the legality and source of these records.
- 4) This was never introduced in court and as mentioned in my email to you earlier today, the prosecution and probation office appear to be trying to have a trial without a jury. Nothing presented here was submitted for trial.

I await your response.

Yours,

Dr. Fleming

FW: response to you

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 7/27/09 8:57 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

Per our conversation today, I understand that you are planning to disagree with everything regarding cases outside of the 10 discussed in court. As we discussed today, the Judge pointed out that this was not a medical malpractice case and the probation office and prosecutors office are continuing to treat it as if it were. As I mentioned again today, the plea states that I did a planar and a tomographic at different times, both with a SPECT camera.

Yours,

Dr. Fleming

RE: Spreadsheet with 78464 figures

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Wed 7/29/09 4:04 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington - Private (dryfly@fvrc.net); Gordon Harrington (gordon.harrington@uni.edu);
Dottie Forsman (dottie@fvrc.net)
Mike,

It would appear, as I have stated several times before, that Ms. Palmer is practicing Medicine by deciding that a second tomographic study is necessary. Both the government witnesses and mine stated this was not the case. I did NOT plea to this and never will. The government is attempting to expand its case and make this medical malpractice. As I have stated several times before, the Judge specifically stated this was not about Medical Practice or Medical Malpractice.

Dr. Fleming

FW: Urgent, please review

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/03/09 11:10 AM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu); Gordon Harrington - Private (dryfly@fvrc.net);
Dottie Forsman (dottie@fvrc.net)
Mike,

As you have instructed me several times, as my attorney, you have directed me not to communicate with the probation office or anyone else on any issues, including finances or other issues, at any time. You have instructed me that you and only you would do that. We have spoken by telephone several times during the last month and you have again directed me to communicate only with you and that you would provide any information required by the probation office or anyone else. You have also told me that violating or rejecting the plea deal would result in the Judge sending me to Jail. In the reports you have attached, it appears to me that there is a question as to the information not being provided to the government and that this would result in a violation of the plea deal. I do not understand! You informed me that you would communicate with them directly providing any and all information required, including but not limited to all the financial information required, which I made available to you before leaving your office after the plea agreement and again since then by telephone. I provided you with all the information they are requesting. Please explain!

Dr. Fleming

RE: Urgent, please review

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/03/09 1:09 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I was unaware that the plea agreement included any such provisions. I am confused; because, what I am reading indicates that they received nothing from you and if this violates the plea agreement, this contradicts your instructions to me and your explanation that the Judge would put me in Jail if I violated the plea agreement. I provided you with all this information and filled out the forms for you to supply to the probation office before I left your office in Lincoln immediately after the plea deal. What happened to it? Please provide me with a list of what you need to complete the requested information by the government. WHAT DO YOU NEED-SPECIFICALLY? As you directed me, I will continue not to respond to the probation office; but, leave that in your hands.

Yours,

Dr. Fleming

voice mail

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/03/09 4:02 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

This is to confirm your voice mail today explaining that you have hard copies of the documents in question; but, that you want them from me in one package. That you are too busy to find the documents and that if I do not have them to you within 48 hours the Judge will hold me in contempt of court, throw out the plea deal and send me to prison.

Dr. Fleming

current status

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Mon 8/10/09 3:53 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

When I left your office, you instructed both Susan and myself to not speak to anyone regarding the plea of guilty. Specifically, that while admitting to billing 78465 instead of 78464, I was not saying this was wrong to do so and that since you had a question as to the actual number of soy participants, that we should plead to this to obtain the no jail time agreement from the government. However, the wording of the Judge (being upset) regarding the financial statements, have me concerned as to whether I am in trouble for following your directive to not respond to the probation officer. What is the current state of affairs and am I in trouble for this?

Dr. Fleming

RE: current status

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Tue 8/11/09 11:12 AM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

You directed me (as my attorney) to not respond to anyone period. My concern is the wording from the Judge where he seems to be thinking I am not providing information, when I have been giving it directly to you to give to the appropriate people, with plenty of time to do so. I filled the probation packet out in your office before I ever left Lincoln after the trial. I do not want the Judge to put me in Jail because I followed your instructions. Regarding the notary. This person knows who I am and has seen my photo ID.

Yours,

Dr. Fleming

> Subject: Re: current status
> To: rmfmd7@hotmail.com
> From: Mike_Hansen@fd.org
> Date: Tue, 11 Aug 2009 08:29:56 -0500
>
> Richard,
> First, whether you were "not saying this was wrong to do so" is
> immaterial. Many people commit crimes that they believe should not be
> crimes. I have no idea who you are blindly copying in on the emails you
> send to me. If denying culpability to a crime you have admitted to makes
> you feel better with yourself then so be it.
>
> Second, I have submitted everything you sent to me. How did you get
> a notary to stamp a document that you did not sign in his or her presence?
> My "directive" was based on your statement to me that probation requested
> the same information that was submitted in the probation packet. The
> current state of affairs is that everything is in the judge's hands and we
> will litigate our objections at the time of sentencing. You are ordered to
> appear in Lincoln on Thursday, August 20, 2009 at noon central daylight
> time.
>
> If you have any other questions before then, do not hesitate to
> contact me.
>
> Mike Hansen
>
>
>
> From: RM Fleming <rmfmd7@hotmail.com>
>
> To: Mike Hansen PD corrected <mike_hansen@fd.org>
>
> Date: 08/10/2009 05:50 PM
>
> Subject: current status

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> Mike,
>
> When I left your office, you instructed both Susan and myself to not speak
> to anyone regarding the plea of guilty. Specifically, that while admitting
> to billing 78465 instead of 78464, I was not saying this was wrong to do so
> and that since you had a question as to the actual number of soy
> participants, that we should plead to this to obtain the no jail time
> agreement from the government. However, the wording of the Judge (being
> upset) regarding the financial statements, have me concerned as to whether
> I am in trouble for following your directive to not respond to the
> probation officer. What is the current state of affairs and am I in
> trouble for this?
>
> Dr. Fleming
>

Re: current status

From: **Mike Hansen** (Mike_Hansen@fd.org)

Sent: Fri 8/14/09 11:06 AM

To: RM Fleming (rmfmd7@hotmail.com)

You are the one that will be ordered by the court to pay a hefty sum in restitution. You know what was asked of you. You provided what you chose to provide in terms of answers. You can see there is some confusion, disgust on the part of the government, probation office and Court as to the extent of your responses. You had better be prepared to answer the Court's questions on Wed. I hold no opinion that I care to share on the legitimacy or lack thereof to your responses to the financial inquiry. The only advice I have given and will continue to give is be truthful.

Mike

Mike Hansen

Assistant Federal Public Defender

100 Centennial Mall North; Room 112

Lincoln, NE 68508

(402) 437-5871

(402) 437-5874 (fax)

From: RM Fleming [rmfmd7@hotmail.com]

Sent: 08/14/2009 10:32 AM MST

To: Mike Hansen

Subject: RE: current status

Mike,

I am not certain if you are wanting me to respond to any of the items from Everett. The federal tax returns have already been received and reviewed by the court handling the divorce.

Yours,

Dr. Fleming

> Subject: Re: current status

> To: rmfmd7@hotmail.com

> From: Mike_Hansen@fd.org

> Date: Fri, 14 Aug 2009 09:38:56 -0500

>

> Here is the state of affairs currently. I am attaching an Order that you

> should be receiving from the court as a hard copy and Everett's response to

> the judge on your submittal to the debtor's exam. Please review and

> respond if you have any questions or concerns. If not, I will see you next

> week. Please show up and hour early so we can talk.

> (See attached file: AE ltr 8-13-09.pdf)(See attached file: Order2

> 8-13-09.pdf)

> Thanks, Mike Hansen

>

>

>

>

> From: RM Fleming <rmfmd7@hotmail.com>

>

> To: Mike Hansen PD corrected <mike_hansen@fd.org>

>

> Date: 08/10/2009 05:50 PM

>

> Subject: current status

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>

> Mike,
>
> When I left your office, you instructed both Susan and myself to not speak
> to anyone regarding the plea of guilty. Specifically, that while admitting
> to billing 78465 instead of 78464, I was not saying this was wrong to do so
> and that since you had a question as to the actual number of soy
> participants, that we should plead to this to obtain the no jail time
> agreement from the government. However, the wording of the Judge (being
> upset) regarding the financial statements, have me concerned as to whether
> I am in trouble for following your directive to not respond to the
> probation officer. What is the current state of affairs and am I in
> trouble for this?

>

> Dr. Fleming

RE: current status

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 8/14/09 12:17 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
Mike,

I thought the court time was Thursday, not Wednesday. Am I wrong?

I provided you with ALL the information you requested and have seen nothing from you to suggest that you are missing or needed anything else. You even called me thanking me for the information and told me you would call me back if anything else was needed. You haven't done so. Since this is the first I am hearing of this, I will respond to you directly, since you have told me to communicate only to you.

While you are not asking me for clarifications, it would appear Mr. Everett is looking for something more from you. I will leave it up to you as to what information you provide him from the below responses.

In response to the items from the August 13, 2009 letter to you from Mr. Everett:

1) (A): Locums is self-employment, not a "Business". The expenses are included for travel, lodging, etc. using the Governments listing for Fed Tax deductions (per diem) based upon where one is at (eg. Des Moines, Poplar Bluffs, etc.). This does not require records, simply noting where one is at and what the government gives for deductions from the government web site.

1) (B): 3171 is a "keep the change" account. I have no idea how they really do this; but, it's the rounding off of payments to put change into an account. I now have \$3.87 in it. 3193 is the credit card which gets used to pay bills I don't have money for in my checking account. I gave you the record I printed off for it.

1) (C): Yes, this is true.

1) (D): You can claim deductions on a vehicle that you are paying for, which you use for business purposes. They don't have a place for "am making payments on a vehicle which the bank owns; but, I hope to someday" It's not being rented, borrowed or leased.

1) (E): What information I have given to you, I have supplied you with. Since I cannot tell from this response what is being talked about, I cannot address it further.

1) (F): Yes, this is true.

1) (G): What was question 17?

2) Because the reimbursement was counted as income which was then taxed. This is added above and beyond. It wasn't simply given to me to repay what I spent. This is included in the 1099.

Yes, the Hummer was driven whatever was recorded. You drive from Reno to Des Moines and back. Do this twice and add all the driving to pick up sons every other weekend (two trips per weekend) and add up all the work miles....

Interest expense were credit card and loans paid.

I have been paying significant attorney fees for the divorce, including all the paperwork, every time I need to return for court, calls and communications regarding abuse to the children, custody issues, etc. this all adds up. Does the court want to discuss the domestic relations litigation costs?

3) This is the same response as above. When reimbursement of something is added to your income (1099), it isn't just giving you money for what you had to pay for.

I am lost on the next question. Yes, I still use the Hummer for business.

Same Attorney fees response as noted for the 2007 question.

The earned income tax credit is for one child according to the divorce agreement.

4) (A): I don't know what question 10 is. This was sent to you.

4) (B): The Dodge Stratus is my son's car. It was given to him for his graduation present and to allow him to get to school, work, etc. when his mother refused to give him a car as she had given our daughter. The 91 Chevy was listed in what I sent you.

4) (C): The entire value of the computer is taken for the year. Computers like so many things are soon outdated making them valueless from a financial view.

4) (D): Rent is \$1300 a month, I have only been able to pay \$900 a month.

If there are still items that require clarification, I will be more than glad to answer them for either you, Mr. Everett or to anyone else's satisfaction. Based upon the above questions, I wonder if this is analogous to your initial responses for me having private counsel, viz. that the government doesn't understand that lawyers in the private sector what their money up front and don't take payments. Similarly, persons who have never been independently employed might not understand it. I have now and continue to provide you with honest, truthful responses, even when you don't believe me and doubt my innocence.

Dr. Fleming

Re: current status

From: **Mike Hansen** (Mike_Hansen@fd.org)
Sent: Fri 8/14/09 12:18 PM
To: RM Fleming (rmfmd7@hotmail.com)
Yes. Thurs the 20th. Sorry for the confusion.
Mike
Mike Hansen
Assistant Federal Public Defender
100 Centennial Mall North; Room 112
Lincoln, NE 68508
(402) 437-5871
(402) 437-5874 (fax)

From: RM Fleming [rmfmd7@hotmail.com]
Sent: 08/14/2009 12:17 PM MST
To: Mike Hansen
Subject: RE: current status

Mike,

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Interest expense were credit card and loans paid.

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Dr. Fleming

Fw: Richard Fleming Sentencing Recommendation

From: **Regina Forshee** (Regina_Forshee@fd.org)

Sent: Fri 8/14/09 12:23 PM

To: rmfmd7@hotmail.com

 1 attachment



FLEMING,R...pdf (29.4 KB)

Richard,

Mike asked that I forward this to you. It is the sentencing recommendation from the probation officer to Judge Kopf. After you look at it, give Mike a call next week if you have any questions.

Thanks.

Regina Forshee
Legal Assistant - Lincoln Office
Federal Public Defender's Office for the
District of Nebraska

FW: Richard Fleming Sentencing Recommendation

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 8/14/09 5:28 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)

 1 attachment

FLEMING,R...pdf (29.4 KB)

Mike,


In reading this document, it sounds like the probation officer is "baring my practice of medicine." I never agreed to this.

Regarding Count XIII, the defendant contracted to complete soy research which he did not complete in accordance with the agreement he had with Physicians Pharmaceuticals. The research results were fabricated. This is not what I plead to.

Dr. Fleming

> Subject: Fw: Richard Fleming Sentencing Recommendation
> To: rmfmd7@hotmail.com
> From: Regina_Forshee@fd.org
> Date: Fri, 14 Aug 2009 14:20:46 -0500
>
>
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>
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> from the probation officer to Judge Kopf.
> After you look at it, give Mike a call next week if you have any questions.
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> Thanks.
>
> Regina Forshee
> Legal Assistant - Lincoln Office
> Federal Public Defender's Office for the
> District of Nebraska
>
> (See attached file: FLEMING,Richard07CR3005rec.pdf)

FW: Richard Fleming Sentencing Recommendation

From: **RM Fleming** (rmfmd7@hotmail.com)
Sent: Fri 8/14/09 5:34 PM
To: Mike Hansen PD corrected (mike_hansen@fd.org)
Bcc: Gordon Harrington (gordon.harrington@uni.edu)
 1 attachment
[FLEMING,R...pdf](#) (29.4 KB)

Mike,

I also didn't plead to the following:

Richard Fleming is pending sentencing on a charge of health care fraud and a charge of mail fraud. Regarding the health care fraud, he billed for multiple tomographic studies of patients hearts when in fact, he completed single tomographic studies. The single study is not sufficient to make a correct diagnosis.

The statement is false.

Dr. Fleming

From: rmfmd7@hotmail.com
To: mike_hansen@fd.org
Subject: FW: Richard Fleming Sentencing Recommendation
Date: Fri, 14 Aug 2009 17:28:33 -0700

Mike,

In reading this document, it sounds like the probation officer is "baring my practice of medicine." I never agreed to this.

Regarding Count XIII, the defendant contracted to complete soy research which he did not complete in accordance with the agreement he had with Physicians Pharmaceuticals. The research results were fabricated. This is not what I plead to.

Dr. Fleming

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> Regina Forshee
> Legal Assistant - Lincoln Office

> Federal Public Defender's Office for the
> District of Nebraska
>
> (See attached file: FLEMING,Richard07CR3005rec.pdf)

CLAYTON BYAM
THOMAS F. HOARTY, III
JOSEPH C. BYAM
SCOTT A. CALKINS

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E-MAIL bh@bhamharty.com

September 28, 2004

Alan Everett, Esq.
Assistant United States Attorney
487 Federal Building
100 Centennial Mall North
Lincoln, NE 68508

Re: Richard M. Fleming, M.D.

Dear Alan:

It is my understanding that you have withdrawn the Subpoena to Testify Before Grand Jury dated September 15, 2004, issued in connection with the requested production of certain records maintained by Dr. Richard Fleming, the Fleming Heart and Health Institute and the Camelot Foundation (collectively referred to herein as my "Clients"). Further, it is my understanding that the subpoena was withdrawn under the agreement that the records in question would be voluntarily produced.

The documents in the possession of my Clients responsive to the requests set forth in the Attachment to the Grand Jury Subpoena are enclosed herein. Some of the documents being produced contain protected health information as defined by HIPAA. My Clients are disclosing this information pursuant to what I reasonably believe to be for a valid law enforcement purpose, and pursuant to a lawful administrative request in lieu of a formal subpoena.

The first set of documents requested relate to the "soy potato chip and weight loss research conducted for Physicians Pharmaceuticals..." My Clients did not perform any studies relating to "soy potato chips." For purposes of responding to your inquiry, my Clients will assume that you are referring to the "soy pasta chip" study conducted at the request of Physicians Pharmaceuticals.

Enclosed herein is a document captioned "Final Study Report for 'Efficacy of Soy Pasta Chips for Weight Loss.'" This document was prepared by Physicians Pharmaceuticals, Inc. Dr. Fleming's signature appears on page 11 of the document and signifies only that Dr. Fleming read the report.

Additionally, in response to the first set of requested documents, I have enclosed herein copies of three checks made payable to the Fleming Heart and Health Institute totaling

102 105 1000 118-752

Alan Everett, Esq.
September 28, 2004
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\$25,000.00. These checks represent the total compensation paid to the Fleming Heart and Health Institute by Physicians Pharmaceuticals, Inc. in connection with the Institute's role in the study at issue.

My Clients are not in possession of any other documents or materials responsive to the first subpart of the Attachment to the Grand Jury Subpoena. The original patient consent forms and patient questionnaires were forwarded to Physicians Pharmaceuticals at the conclusion of the study. It is my understanding that a number of the patients participated in the study anonymously, and declined to execute patient consent forms and/or patient questionnaires. Any additional documents that my Client had maintained in connection with this study were previously forwarded to Susanne Rydberg at the Nebraska Department of Health and Human Services.

In this particular study, no peer review board was employed. Therefore, there are no peer review board members who provided research oversight.

The second set of documents involves a broad request for "Identification of all female patients and original patient consent forms involving the Breast Enhanced Scintigraphy Test, a/k/a B.E.S.T." As you are likely already aware, Breast Enhanced Scintigraphy Testing (BEST) combines myocardial and breast-imaging technologies into a single test that yields diagnostic information about myocardial function and distinguishes between normal breast tissue, inflammatory breast tissue and carcinoma of the breast. The majority of patients who were seen by my Clients for breast related issues underwent BEST testing. Therefore, virtually all of my Clients' medical files involving female patients seen for breast related issues would contain at least some information responsive to this request.

You will find enclosed herein black-and-white images, which are copies of documents in my Clients' immediate possession demonstrating medical treatment and research that they performed utilizing the BEST technology. The images identify, in most cases, the first initial and last name of the patient that is the subject of the particular image.

We anticipate that a review of my Clients' patient files, relating to those patients who were seen for breast related conditions, would contain similar, and in many cases identical, materials. As my Clients are no longer actively operating in Nebraska, the original patient files have been placed in storage. If you would require my Clients to produce all patient files containing BEST images, please let me know. I will attempt to arrange to have those files produced. Additionally, certain documents responsive to this request are believed to have been produced to Ms. Susanne Rydberg of the Nebraska Department of Health and Human Services on or about August 23, 2004, and my Clients have not retained copies of any of those documents.

To determine whether soy protein has any effect on inflammatory changes of the breast, forty women with inflammatory breast changes, as defined by the BEST imaging referred to in the preceding paragraph, were asked to consume soy protein daily and were restudied 6 months later. Of these 40 women, 30 were studied both before and after 6 months of soy protein

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Alan Everett, Esq.
September 28, 2004
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consumption. Each of these studies were conducted in the women's normal course and treatment. It was found that there was a statistically significant difference between the inflammatory changes noted before and after soy protein consumption. These findings were subsequently published in a peer review medical journal.

Because the testing was performed in the normal course of medical treatment, as opposed to in a pure research setting, no patient consent forms involving the BEST soy related study were obtained. Any materials relating to the care, study and treatment of women with breast conditions by my clients would be retained in the normal course of business in each of the patients medical files. No individually identifiable health information was disclosed by my Clients in conjunction with the BEST soy related study.

If additional information or clarification of the statements set forth herein is required, please feel free to contact me.

Very truly yours,

BYAM & HOARTY



Scott A. Calkins

SAC:tbx
Encl.

Soy Chip Data: Examination for Anomalies

Mark S. Kaiser and Alicia L. Carriquiry

Department of Statistics

Iowa State University

March 2009

1 Background

This report contains a statistical examination of data from a study titled “Efficacy of Soy Pasta Chips for Weight Loss”, conducted in 2004 at the Fleming Heart and Health Institute of Omaha, Nebraska. Our understanding is that questions have been raised about the authenticity of the data produced by that study and, specifically, whether some of those data may have been fabricated. Statistical examination of a set of data cannot “prove” or “disprove” falsification of data records in an absolute sense, but it can determine whether certain types of anomalies exist that would not be expected in data from most scientific studies. The goal of this exercise was to uncover any such anomalies that might exist in the data from this study.

The data used in this analysis were taken from a final report signed by the principal investigator on 7 April 2004 and provided to us via electronic transmission by Dr. Richard Fleming. The data contain records for 60 individuals that consist of values for height, initial weight, weight at two weeks, weight at four weeks, and body mass index at the same time points as weight. Our examination of these data makes use of only the directly recorded variables of height and the three weight measurements.

2 Methods of Examination

Appropriate statistical methods for examination of data to detect potential fabrication depend on the characteristics of the study or studies of concern, including study design, objectives, and the analysis used to reach conclusions. Also important is the type of data fabrication suspected. The best methods for detection of one or a few fabricated data records differ from those more appropriate for the detection of wholesale fabrication of an entire or nearly an entire data set (e.g., Buyse *et al.* 1999). The study of concern here was of a very simple design with

apparently self-selected subjects and lacking multiple medical centers or treatment groups, precluding the use of comparison of multiple centers or a suspect data set to an unsuspicious one (e.g., Al-Marzouki *et al.* 2005). The examination reported here focused on three aspects of the data records, *marginal and joint data structure*, *recorded data values*, and *influence on results*. The motivation for considering these aspects of the problem are described in this section.

Fabrication of data generally has a specific objective, either to influence the outcome of data analysis (e.g., show an effect of one or more treatments) or to avoid the effort needed to properly conduct data collection if a pattern seems clear from an analysis of some actual data. The former situation may result in alteration of one or more data records that have disproportionate influence on the outcome of statistical analysis for the study. Alternatively, if an entire data set is fabricated to exhibit an effect of some type (e.g., a difference in treatment group means), other characteristics of typical data sets that might also show such an effect (e.g., variance or covariance structure) are difficult to match. That is, most scientists cannot *preserve* higher-order structure in falsified data while achieving the desired first-order differences (Haldane 1948). The fabrication of data records as a matter of convenience may sometimes be detected based on either the number or distribution of digits in recorded data (e.g., Walter and Richards 2001). For example, the presence of “extra” digits in recorded data may indicate that other, possibly legitimate, records have been averaged to produce the falsified data, or a fabricated data set may contain a preference for certain digits in either the first or terminal places. This latter phenomenon is related to the fact that the human mind is a poor random number generator.

While a comparable data set from an undisputed study is not readily available for this analysis, it is possible to make use of theoretical probability distributions for comparison with the Fleming data set. Simulation of random values from theoretic-

cal probability distributions can be used to describe the expected behavior of actual data. Serious departures from such behavior are then a signal that something may be amiss in a given set of values. The Soy Chip study resulted in a four-dimensional multivariate observation for each subject, height, weight 0, weight 1, and weight 2. Assuming (which can be reasonably verified for the Fleming data) that a multivariate normal distribution provides a good model for the joint data characteristics, simulated values from this distribution can be used to examine what might be expected in terms of recorded data values (e.g., terminal digits) and whether or not averaging results should appear in randomly generated data.

3 The Effects of Self-Selected Samples and Study Design

Before proceeding to examination of the actual data values it is helpful to identify the effects of two inter-related aspects of the study under discussion, those being the self-selection of subjects who participated in the study, and the lack of a study design that would allow conclusions about the effect of soy chips on weight loss.

3.1 Self-Selection and “Expected” Data Values

A common-sense and, in fact, quite legitimate source of suspicion about a set of data values is if they appear “too good to be true”. In some respects that seems to hold for the data under examination here. All but one of the subjects lost weight, at an average of over 3 pounds per two-week period. The “treatment” of soy chips appears, at first glance, to have produced remarkable results in terms of weight loss, perhaps as much as many of us could rationally attribute to some type of active weight loss regimen, yet alone simply an alternative snack food. The reason, in

this case, that this aspect of the study fails to provide evidence that something is amiss in the data is that the subjects were self-selected for participation. There is little information in the final project report as to how subjects were recruited for the study, other than that being “motivated to lose weight” was one of the inclusion criteria. Put simply, it is not known what else these subjects were doing in attempts to lose weight. It is not known if they became aware of the study through social contact with other study participants (e.g., at health clubs or gyms or weight loss support groups), what characteristics they may have or may have not shared in common, what their overall diets consisted of, what they may have stopped eating if they ate soy chips instead, how much physical activity they engaged in, or any of a host of other factors that might have influenced the results of the study. It is not even known if they actually consumed the soy chips. The implication is that no results can be considered too “good” or too “bad” to be true, unless those results are outside of the realm of physical possibility.

An additional effect of the self-selection of subjects for the study is that comparisons of marginal distributions of, for example, height and initial weight, with what might be expected from a random sample of the population at large lose all meaning. It should not necessarily be expected that the distributions of height or initial weight are consistent with a random sample from the population, or that the relation between height and initial weight should be consistent with such a sample. In fact, it might be argued that, because the subjects in the study were “motivated to lose weight”, the relation between height and initial weight should differ from the population at large, containing a greater proportion of individuals with weight on the higher end of the distributions of weight for a given height. There is, in this case, simply no appropriate “reference group” against which to compare the data values.

3.2 Study Design

Although the final study report described the study as a “randomized clinical trial”, there exist no factors that could have been randomized. There was no control group (i.e., individuals not given soy chips), nor any alternative treatment group (e.g., apples as snacks); note that a true placebo (i.e., “fake” soy chips) or double-blind study design would be difficult to devise in this setting. Because it is not known what behaviors subjects were engaged in during the study, and there is no group that could be reasonably expected to have engaged in the same behaviors other than the consumption of soy chips, there is no scientific evidence that soy chips had any effect at all on the results. From a scientific viewpoint, the evidence in the data that being handed free soy chips promotes weight loss is exactly the same as the evidence that consuming soy chips promotes weight loss. In fact, the evidence that visiting the Health and Heart Institute to be weighed promotes weight loss is exactly the same as the evidence that consumption of soy chips promotes weight loss, which is to say there is no scientific evidence for any of these conclusions.

In the opinions of the authors of this report, a manuscript based on this study would not be accepted for publication in any scientific journal. The potential relevance of this for the current exercise is in terms of the objective of data fabrication in this study, as mentioned in the previous section. Any individual with an advanced degree in a scientific discipline, or at the very least any individual who has successfully published a paper in a scientific journal, should understand the shortcomings of the study design. The objective of data fabrication in this situation would then almost necessarily be one of convenience rather than career development, that is, simply to avoid the time and energy needed to collect actual observations. Common sense, as well as formal logic, then suggests that the time and energy needed to falsify data records should be no more than (and, given the anathema with which data fabrication is viewed in the scientific community, perhaps even considerably less

than) the time and energy needed to make actual observations. The only alternative I can think of regarding motivation for data falsification in this situation is pleasing a client from whom a substantial amount of additional funding is anticipated but, if it becomes clear to the client that the study was largely without scientific merit because results cannot be published, this would seem a remote possibility.

4 Marginal and Joint Data Structure

The first approach used in this exercise was to examine the marginal and joint data structures for the entire set of data. This examination might indicate the presence of records that were altered in a manner that failed to preserve the overall coherence (or general behavior) of the collection of data in a manner consistent with typical probabilistic rules. For example, if a number of records were falsified for a particular weight (e.g., weight2 at week 4) they might stand out as having a different relation with height than they did at an earlier stage (e.g., weight1 at week 2). If entire data records were falsified the relation among variables in those records (ht, wt0, wt1, wt2) may not follow the overall pattern of the set of data. In a sense, then, this examination is one of *data consistency*. An individual falsifying a few data records would need to take care that those records “fit” the general pattern in the entire data set. An individual falsifying the bulk of records or fabricating an entire data set would need to take care that those records were both biologically consistent and probabilistically consistent. Probabilistically consistent here means that there should exist some joint probability distribution that could have “generated” the observed data. While no theoretical probability distribution is “correct” in a real problem, real data tend to follow the patterns of data simulated from theoretical distributions and dictated by the rules of probability. Falsified data often fail to exhibit this same consistency (unless, of course, they were produced via simulation

from theoretical probability distributions). Basic summary statistics for the Fleming data set are presented in Table 1.

There is a basic consistency in these summary values. Variances for the three

Variable	Min	Q1	Q2	Q3	Max	Mean	Variance
Height	60.50	63.94	66.00	68.44	76.00	66.32	10.439
Weight0	146.0	165.1	185.0	205.5	301.0	193.71	1409.587
Weight1	139.0	162.2	182.5	201.6	295.0	189.76	1370.250
Weight 2	128.5	159.5	179.0	199.0	293.0	186.41	1357.250

Table 1: Basic summary statistics for the Fleming data.

weight values are not dramatically different, and a decrease in weight is seen for various quantiles in a consistent manner. There is perhaps a surprising difference between the minimum weight at times 2 and 1, that difference being -10.5 pounds. The minimum weights at times 1 and 2 correspond to the same individual. To see if this should be considered an extreme value, inconsistent with the overall data structure, a set of data was simulated from a multivariate normal distribution with means and variances that match the values of Table 1. The minimum values for “weight1” and “weight2” in these simulated data also corresponded to the same data record (i.e., the same simulated “individual”) and the difference was -9.7 . While not demonstrating that the one actual data record could not have been fabricated, this does demonstrate that the occurrence would not be unexpected under a typical probabilistic structure of the kind used to model data.

Correlations among the variables of height, weight0, weight1 and weight2 are reported for the Fleming data in Table 2. Extremely high correlations (for which the values of correlations between weight0, weight1, and weight 2 would qualify) are sometimes taken as an indication of results “too good to be true” (e.g., Akhtar-

Danesh and Dehghan-Kooshkghazi 2003). But that is a weak argument against the Fleming data set in this case, partially because of the self-selection of study participants as discussed in the previous section of this report, and partially because of a combination of the ranges for weight measurements in Table 1 and the physiological realities of how much weight an individual can gain or lose in a period of several weeks. Correlation is a measure of linear association between two variables and this measure is affected by the range of values considered. A wide range of initial values (e.g., a range of 155 lbs. in weight0 for comparison with weight1 or a range of 156 lbs in weight1 for a comparison with weight2), coupled with the biological reality that any individual is unlikely to lose or gain more than a small fraction of their initial value *relative to the initial range* indicates that high correlations are to be expected in this situation. The Fleming data are also consistent with the anticipation that weights observed at more distant time points (i.e., weight0 and weight2) should still be correlated, but somewhat less highly correlated than weights observed at less distant time points (i.e., weight0 and weight1).

	ht	wt0	wt1	wt2
ht	1.0000000	0.5263469	0.5274059	0.5289093
wt0	0.5263469	1.0000000	0.9989028	0.9961254
wt1	0.5274059	0.9989028	1.0000000	0.9983947
wt2	0.5289093	0.9961254	0.9983947	1.0000000

Table 2: Correlations for the Fleming data.

Scatterplots of weights at times 0, 1 and 2 against height are presented for the Fleming data in Figure 1. The first thing to note here is the similarity of the three scatterplots. This should be expected, again because of the total range of weights contained in the data sets and the physiological realities of how much weight can change for humans over a period of several weeks. It appears that one could pick

out individuals on these plots and that is, in fact, true. What would be disturbing would be to find individuals with radically different positions on one or more of the three plots, and that does not occur. One may also notice that there are more widely scattered points above the bulk of the data pattern than there are below. This is not necessarily unexpected, because the self-selected sample of participants were individuals who considered themselves overweight. Statistically, this data pattern suggests distributions of weight for given heights that are skew right rather than symmetric.

Overall, there is little in the set of data values examined to suggest that they could not be the result of a study with an absence of fabricated data. The data values may be considered as *internally consistent*. At this point we would have no justification for suggesting that the data have been manipulated in a manner consistent with the falsification of data. Examination of data in the manner of this section, however, is not a powerful approach for identification of anomalies because of the lack of a reference for comparison. As indicated previously, the population as a whole will not serve this purpose because subjects in the Fleming study were not intended to be a random sample from the population, and we lack data from a comparable undisputed study for comparison as well. What we can say is that the data set fails to contain obvious glaring inconsistencies that would suggest fabrication of data.

5 Recorded Data Values

Any numerical data value consists of a sequence of digits. For example, the value of 156 for an initial weight in this study has the digits 1, 5 and 6, in that order. There are two common approaches for examination of recorded digits in data records – investigation of recorded values that contain “extra digits”, and comparison of

distributions of the values 0 through 9 in various places in the data (e.g., first digit or last digit). We consider these two approaches in turn.

5.1 Records with Extra Digits

The majority of the data contained in the Fleming data set are recorded to the nearest whole number (i.e., height to the nearest inch, weight to the nearest pound) but there are a number of records that contain extra digits of either 0.25, 0.5 or 0.75. Table 3 presents the frequencies of these extra digits for the four observed variables.

Extra Digits	Height	Weight0	Weight1	Weight2
0.25	5	0	0	0
0.50	9	11	9	3
0.75	4	0	0	0

Table 3: Frequency of extra digits in the Fleming data.

Data records with extra digits relative to the majority of the data may indicate that other data records were averaged to produce the suspect record (e.g., Walter and Richards 2001). For example, if two records with weights of 174 and 177 are averaged the result is 175.5, and the extra digit is easily recorded by an individual falsifying data. Of course, the mere presence of extra digits in some records does not necessarily indicate the record was constructed, but in the absence of falsification it would be unusual for one (entire) record to be the average of two others, even more unusual for this to be true of two records, and so forth. In the Fleming data there are four variables, giving rise to four possible places where data averaging may have occurred to produce false data. A computer function was written (see Appendix 1) that took each record with extra digits for height and compared values of the

four variables to averages of all other unique pairs of records (of which there are $59(58)/2 = 1711$). Each instance in which any of the variables in the “suspect” record with extra digits was found to correspond to the average of two other records was saved. Of the 18 suspect records in the Fleming data, pairs of other subjects were found such that the average of exactly one variable in those records matched the value in the suspect record in 17 cases. For 12 of the suspect records pairs of other subjects could be found that, when averaged, produced the values in the suspect record for exactly 2 variables. But for none of the suspect records was it possible to locate a pair of other subjects that when averaged produced 3 or all 4 of the variables in the suspect record. The results for suspect records having at least two variables equal to the average of other records are presented in Table 4. In this table, the column labeled “suspect” gives the subject number from the original data corresponding to a data record having extra digits for height. The columns labeled “other 1” and “other 2” give subject numbers from two other records that were found to average to the suspect record value for two or more of the variables. The column labeled “nflags” gives the number of variables (out of the 4 possible but at least 2) for which the two other records produced averages equal to what was reported for the suspect record, and the columns labeled “flag1” through “flag4” give the specific variables for which averages matched the value of the suspect record (flag1=height, flag2=weight0, flag3=weight1 and flag4=weight2).

There are several aspects of the results in Table 4 that are of interest.

1. Note first that there are quite a few of the records with extra digits for height (12 out of 18 to be exact) that have at least two variables equal to the averages of two other records in the data set, but there are none that have all four variables equal to the average of two other records.
2. Curiously, many of the suspect records in Table 4 contain variables that have values equal to the average of more than one pair of other records (e.g., suspect

suspect	other1	other2	nflags	flag1	flag2	flag3	flag4
1	17	28	2	1	0	1	0
1	17	33	2	0	1	1	0
1	28	55	2	0	1	0	1
1	34	36	2	0	1	1	0
2	12	28	2	0	1	0	1
2	27	30	2	0	0	1	1
2	27	58	2	0	0	1	1
6	24	48	2	0	1	1	0
6	42	48	2	0	1	1	0
8	6	10	2	0	1	1	0
8	9	28	2	0	1	0	1
8	38	48	2	0	1	1	0
8	50	59	2	0	1	1	0
10	34	55	2	1	0	0	1
11	53	55	2	0	1	1	0
13	25	40	2	0	1	0	1
22	44	55	2	0	1	1	0
26	17	29	2	0	0	1	1
28	3	33	2	0	1	1	0
28	27	56	2	0	0	1	1
28	27	59	2	0	1	1	0
28	41	60	2	0	0	1	1
28	50	59	2	0	1	0	1
28	53	58	2	1	0	0	1
34	25	60	2	0	1	1	0
34	26	39	2	0	1	1	0
34	39	49	2	1	0	0	1
35	12	43	2	1	0	1	0
35	12	59	2	1	1	0	0

record 1, 2, 6, 8).

3. The number of suspect records that have values equal to averages of other records seems more prevalent for weight variables than for the variable of height.
4. There are no suspect records that are the same in total (i.e., for all four variables) to averages of other records. In fact, there does not appear to be a simple pattern for which variables are averages of other records. For example, subject numbers 17 and 28 as well as subject numbers 17 and 33 average to the value of weight1 for subject number 1. Subject numbers 17 and 28 also average to the height value for subject 1, but subject numbers 17 and 33 do not, while subject numbers 17 and 33 average to the value of weight0 for subject 1 but subject numbers 17 and 28 do not.

Overall, the results of Table 4 indicate that, if the suspect records with extra digits for height in the Fleming data were constructed using a process of averaging other data records, this was done according to some complex system that is difficult to uncover. For example, subject 1 had matches (i.e., flags) that involved subject numbers 17, 28, 33, 55, 34 and 36. The record for subject 1 was not a match for the average of any 3 of these other records (of which there are 20), any 4 of these records (of which there are 15), any 5 of these records (of which there are 6) or all 6 of the records. The number of instances in which some variables in the records for which height contained extra digits turn out to be equal to averages of other records is, however, curious.

To examine whether or not the phenomena of Table 4 should be considered "out of the ordinary", we compared the results given in that table with data generated randomly from a coherent probabilistic structure. To accomplish this, 60 records were simulated from a four-dimensional multivariate normal distribution

with means, variances, and covariances equal to the realized values from the Fleming data set. This data set, then, was simulated to match the marginal and joint data structures of the Fleming data set, but to be a case in which other aspects of the data followed a typical probabilistic structure difficult for humans to duplicate if asked to purposely falsify data (this entire simulated data set is contained in Appendix 2). The four variables in the simulated data will be called height, weight0, weight1 and weight2, in analogy with the actual problem. Each simulated record was then rounded to the nearest whole number. Following the frequencies of Table 3, 18 values for the variable height were randomly selected to have an extra digit added to their values; to 5 records the value of 0.25 was added, to 9 records the value of 0.50 was added, and to 4 records the value of 0.75 was added. In addition, 11 records were randomly selected to have a value of 0.50 added to weight0, another 9 records randomly selected to have a value of 0.50 added to weight1, and 3 records were randomly selected to have a value of 0.50 added to weight2. Running these simulated data through the same computer function used to produce Table 4 from the Fleming data gave the results presented in Table 5.

Although there is a minor difference between the values of Table 5 and those from the Fleming data of Table 4 (i.e., 7 of the 18 “suspect” records in the simulated data matched averages of other records in 2 or more variables, while 12 of 18 did for the Fleming data) the patterns are remarkably similar. In fact, the second, third, and fourth characteristics of the data in Table 4 listed previously, which may have seemed suspicious, were reproduced nearly identically in the simulated data results of Table 5.

Neither Table 4 nor Table 5 report the number of “suspicious” records matching averages in only 1 of the four variables. A table of frequencies for the number of suspicious records (out of 18 for both the Fleming and simulated data) that had 1, 2, 3, or 4 of the variables height, weight0, weight1, and weight2 matching averages

suspect	other1	other2	nflags	flag1	flag2	flag3	flag4
25	16	58	2	0	1	1	0
33	11	58	2	1	1	0	0
34	15	57	2	0	1	1	0
34	17	57	2	1	1	0	0
34	49	58	2	0	1	0	1
39	1	50	3	0	1	1	1
39	2	57	2	0	1	1	0
39	32	35	2	0	0	1	1
42	5	24	2	0	1	1	0
42	22	35	2	0	0	1	1
42	28	49	2	0	1	0	1
42	37	38	2	0	0	1	1
50	1	30	2	0	1	0	1
59	25	34	2	0	1	0	1

Table 5: Data records in a simulated data set with heights recorded with extra digits for which variables were found to equal averages from two other records.

of pairs of other data records is presented in Table 6. An ordinary Chi-squared test of differences for these frequencies is not appropriate here as the entries in Table 6 are not independent (i.e., a given suspicious data record could have matches with multiple pairs of other records, some pairs matching 1 of the variables and other pairs matching 2 of the four variables). In addition, only one simulated data set is presented and other simulated data sets would vary from this one to some degree. The point of Table 6, however, is that it does not appear that the Fleming data are at all unusual compared to what might result from a completely random probabilistic mechanism with the same marginal and joint data characteristics. The only conclusion that seems plausible is that the patterns exhibited in the Fleming data and reported in Table 4 are entirely in concert with what might occur from a completely probabilistic structure matched to the marginal and joint structures of those data.

Data Set	No. of Variables			
	1	2	3	4
Fleming	17	12	0	0
Simulated	14	7	1	0

Table 6: Frequency of matches for “suspicious” data records with averages of other pairs of records for the Fleming and simulated data sets.

5.2 Distributions of Digits

There exist demonstrated distributions for the frequencies with which different digits (0 through 9) appear in data from various sources. There is a result known as *Benford’s law* that indicates the relative frequencies of leading digits in data should follow an approximate logarithmic distribution (e.g., Buyse *et al.* 1999, Hill 1998).

This approximation often applies to financial data and other data consisting of an aggregation of various sources but does not typically apply to scientific data from a single data source (e.g., Hill 1998). In fact, a demonstration that Benford's law corresponds to a coherent probabilistic structure made use of random digits selected from random distributions (Hill 1996), a context that does not apply to most scientific investigations. The emphasis put on Benford's law by, for example, Buyse *et al.* 1999 seems misplaced, except perhaps in the examination of financial records for medical facilities.

The other use of distributions of digits in data to detect anomalies rests on the assumption that recorded data values may contain meaningful and nonmeaningful digits. The leading (first) digits of data values are often meaningful in indicating the magnitude of responses. The trailing (last) digit or digits are often nonmeaningful in this regard. For example, in a weight difference of 190.3 and 185.6 pounds, the first three digits of 190 and 185 are more meaningful than are the trailing decimal digits of 3 and 6. It is often assumed then that the meaningless digits should follow a uniform distribution on the discrete integer values from 0 to 9 (e.g., Walter and Richards 2001). Because the human mind appears to be a poor random number generator, fabricated data may often show a distribution of meaningless digits substantially different from a uniform distribution. But, as pointed out by O'Kelly (2004), data with non-meaningful trailing digits do not occur in many clinical trials, and that is the case here, except for perhaps the data records with extra recorded digits which have already been examined in the previous subsection. Hill and Richards (2002) also point out a number of potential pitfalls in testing digits, particularly in the absence of an unquestioned reference data set. It may remain true, however, that the last digits in a fabricated data set (even with most records recorded to the nearest whole number) would be difficult for a human to match to a probabilistic structure. Thus, if there is a use to be made of examining the distributions of digits

in the Fleming data it would involve the final whole digit.

In order to demonstrate what an examination of trailing digits would suggest about the Fleming and simulated data sets, a computer function was written to give the frequency of final digits (as whole numbers – data records containing extra digits first had those digits removed) for each of the variables of height, weight0, weight1, and weight2, and to test the resultant empirical distributions against a theoretical uniform distribution. The results for the Fleming data are presented in Tables 7 and 8.

Digit	ht	wt0	wt1	wt2
0	6	8	7	8
1	5	4	2	5
2	7	4	3	5
3	6	5	6	6
4	4	7	8	6
5	8	6	7	9
6	7	4	9	3
7	6	5	7	7
8	6	10	4	5
9	5	7	7	6

Table 7: Observed frequencies of final digits in the Fleming data.

Under an assumption that the relative frequencies of final digits (0 through 9) should follow a uniform distribution, the expected frequency for each digit is, with 60 observations $60/10 = 6.0$. Standard Chi-squared tests of goodness of fit for such a uniform distribution to the values in Table 7 yields the results of Table 8. Clearly, none of the variables contain distributions of final digits having evidence of departure from a uniform distribution.

Variable	Test Statistic	p -value
Height	2.00	0.9915
Weight0	6.00	0.7399
Weight1	7.67	0.5680
Weight2	4.33	0.8881

Table 8: Test statistics and associated p -values for testing that the frequencies of final digits in the Fleming data differ from a uniform distribution.

Repeating this exercise with the data simulated from a multivariate normal distribution yields the observed frequencies of Table 9 and the associated test statistics and p -values of Table 10. These simulated data, as they should, also offer no evidence of a departure from a uniform distribution of final digits for any of the four variables.

Digit	ht	wt0	wt1	wt2
0	5	2	7	7
1	6	12	4	4
2	5	7	7	9
3	6	5	4	3
4	4	4	5	11
5	8	6	5	5
6	9	5	8	8
7	8	7	8	8
8	4	5	7	3
9	5	7	5	2

Table 9: Observed frequencies of final digits in the simulated data.

Variable	Test Statistic	p -value
Height	4.67	0.8623
Weight0	10.33	0.3242
Weight1	3.67	0.9320
Weight2	13.67	0.1345

Table 10: Test statistics and associated p -values for testing that the frequencies of final digits in the simulated data differ from a uniform distribution.

The upshot of this subsection is that, in the first place, the examination of of the Fleming data for assumed distributions of digit values in leading digits is problematic on theoretical grounds, although it is less so for trailing digits. Weights should not have leading digits less than 1 for overweight individuals (i.e., less than 100 pounds) and would be unlikely to have leading digits greater than 3. The distribution of final or trailing digits should not follow Benford's law because they do not correspond to observations from multiple sources. An examination of the Fleming data demonstrates that the distribution of trailing digits appears entirely consistent with what would be expected from a coherent probabilistic structure, which the simulated data are know to follow.

6 Could the Fleming Data Be Simulated?

The agreement of the Fleming data with values simulated from a multivariate normal distribution in terms of the averaging phenomena discussed in section 5.1, and the distribution of trailing digits in Section 5.2, raises the question of whether the data could have been produced wholesale (i.e., in entirety) from the use of a random number generator. The most likely candidate for such simulation would be a multivariate normal distribution with marginal and joint characteristics equal to

the means, variances, and covariances reported for the Fleming data and described in Section 4 of this report. Given a moderate amount of statistical sophistication, many individuals could produce such a data set. That this is unlikely to be the case in the current situation is evidenced by the failure of marginal distributions of `weight0`, `weight1`, and `weight2` to follow univariate normal distributions. A known property of multivariate normal distributions is that the marginal distributions corresponding to individual variables are univariate normal in form. Figure 2 presents histograms of the marginal distributions of `weight0` for the simulated data set in the upper panel and the Fleming data set in the lower panel. The simulated data (upper panel) exhibit a distribution consistent with a normal theoretical distribution, which they should. The Fleming data (lower panel) exhibit a distinct skew right distribution, consistent with the observation of the scatterplots of weight versus height in Figure 1 (see Section 4 of this report). Is it possible to simulate data that have the characteristics of the Fleming data set? The answer is yes, it is possible, but doing so would require the ability to preserve means, variances, and correlations as described in Section 4 of this report, preserve the averaging property described in Section 5 of this report, and produce the difference in marginal distribution of weights at time 0 given in Figure 2. There exist ways to achieve all of this but they require a relatively high level of statistical knowledge, including the time and ability to write computer functions for tasks that are not readily available in pre-packaged routines.

7 Influence on Results

Falsification of data often has the objective of producing certain results in a data analysis. Quantification of the *influence* of each observation on the resultant analysis can then sometimes highlight one or a group of observations that played a large role

in determining the outcome and conclusions of a study. While not in any manner evidence of falsified values by themselves, the occurrence of high influences can suggest cases worthy of additional examination. In the report on results of the Fleming study provided to us, the analysis consisted of two paired t-tests, one conducted on the difference in weight0 and weight1 values and the other conducted on the differences in weight1 and weight2 values. To examine the influence of recorded data values on these tests observations were deleted one at a time from the data, the test statistic recomputed without that value, and the difference (absolute value) of that deleted-case statistic with the test statistic computed using the entire data set was calculated. This value then provides an indication of the influence of individual observations on the test conducted with the entire set of values. A summary of the influence values produced using the Fleming and simulated data for the comparison of weight0 and weight1 values is presented in Table 11, and the same is reported for the comparison of weight1 and weight2 values in Table 12.

Data Set	Min	Q1	Q2	Q3	Max
Fleming	0.0223	0.1758	0.2461	0.3079	2.8390
Simulated	0.0211	0.1309	0.2784	0.3265	0.9403

Table 11: Summary of influence values for comparison of weight0 and weight1 records.

Data Set	Min	Q1	Q2	Q3	Max
Fleming	0.0111	0.1564	0.1833	0.2376	1.306
Simulated	0.062	0.1794	0.2491	0.2818	0.5538

Table 12: Summary of influence values for comparison of weight1 and weight2 records.

The most notable feature of both Table 11 and Table 12 is the extreme distance between the third quartile (or 75%–tile, denoted Q3) of influence values and the maximum influence value for the Fleming data. Stem and leaf plots demonstrate that this is due to only one extreme value that is hugely separated from the remainder of the data. For example, the influence values for the Fleming data of Table 11 have the following stem-and-leaf plot:

The decimal point is at the |

[illegible]

The data record that corresponds to the single observation with influence value 2.8 (which is just over 9 times larger than the next largest value) corresponds to subject 52 having height= 66, weight0= 186, weight1= 189 and weight2= 192. This subject gained weight between each weighing. The result is that, while highly influential relative to any of the other data records, the results for this subject decreased the size of the test statistic and hence the significance of the overall findings of the study. If this record was falsified the only reasonable objective would have been to purposely introduce one outlier into the data to make it look more

“real”, not to produce a desired result in the analysis of the study. This same observation is also the one extreme influence value for the Fleming data from Table 12.

8 Conclusions

As stated in the opening paragraph of this report, a statistical examination of data cannot definitively prove or disprove the falsification of data records. The analysis conducted in this report, however, does allow the following conclusions to be reached.

1. If the Fleming data were falsified it would appear that they were fabricated in a nearly wholesale fashion, that is, more-or-less in total. These data are internally consistent, consistent with the behavior of values simulated from a theoretical probability distribution, and there is only one data record with undue influence on the results of the study (and this influence was in the “wrong” direction).
2. Because of the properties listed in conclusion 1 and, in particular, the averaging behavior described in Section 5 that the Fleming data shared with simulated data, the most likely mechanism for fabrication in this study must be considered simulation from some theoretical probability model.
3. Because of the multivariate nature of the four recorded data values for each subject, maintaining internal consistency would require, or at least strongly suggest, that a multivariate probability distribution would need to have been employed to simulate data values. The candidate most readily available to non-statisticians (and even to statisticians without extensive experience in the construction of multivariate distributions from other probability structures) is the multivariate normal distribution.

4. The marginal moments (means, variances) and joint moments (covariance or correlation) of the Fleming data could easily be maintained through simulation from a multivariate normal distribution. However, the skew shape of marginal weight distributions (e.g., Figure 2) could not.
5. Combining items 1 through 4 immediately above suggests that, if the Fleming data were fabricated, the procedure used to arrive at the reported values was necessarily complex, requiring considerable statistical expertise and time to conduct. If it were supposed that the most likely motivation for data fabrication in this situation was to save time and effort relative to actually performing the observational process, this would seem at odds with what would have been needed for fabrication of the data.

Overall, there is simply no data-driven evidence that the Fleming data set is other than would be expected under a legitimate study. Haphazard falsification would be unlikely to result in the consistency of behavior these data show with a coherent (probabilistically consistent) probability distribution. One would need to simultaneously preserve the proper behavior of 6 correlations (ht-wt0, ht-wt1, ht-wt2, wt0-wt1, wt0-wt2, wt1-wt2), averaging properties, and distribution of trailing digits. That all of this could be produced by a human with a pencil and paper would be unusual, although it could result from simulation using the proper computer package. Simulation from a multivariate normal distribution could control all of these characteristics, which to statisticians depend on what are called the *first two moments* of distributions, in a consistent manner. Achieving this while at the same time producing marginal distributions that depart from those associated with a multivariate normal distribution in shape, which depends on what statisticians call *higher-order moments* would require considerable statistical ability as well as considerable time and effort.

9 Literature Cited

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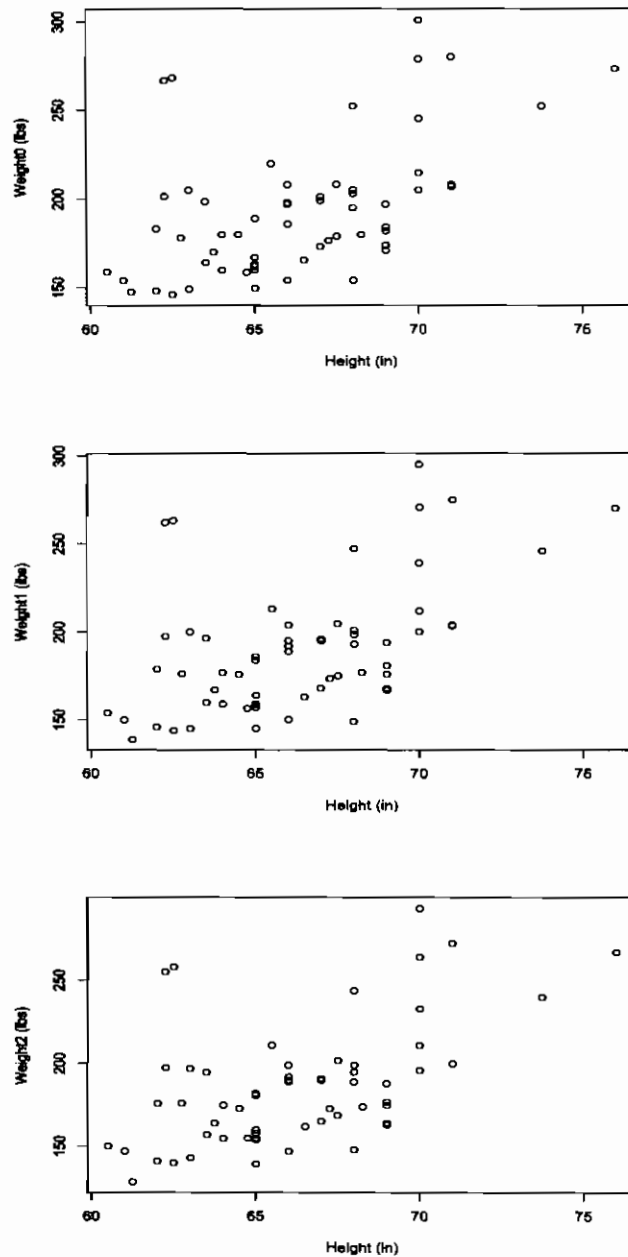


Figure 1: Scatterplots of weights against heights for the Fleming data.

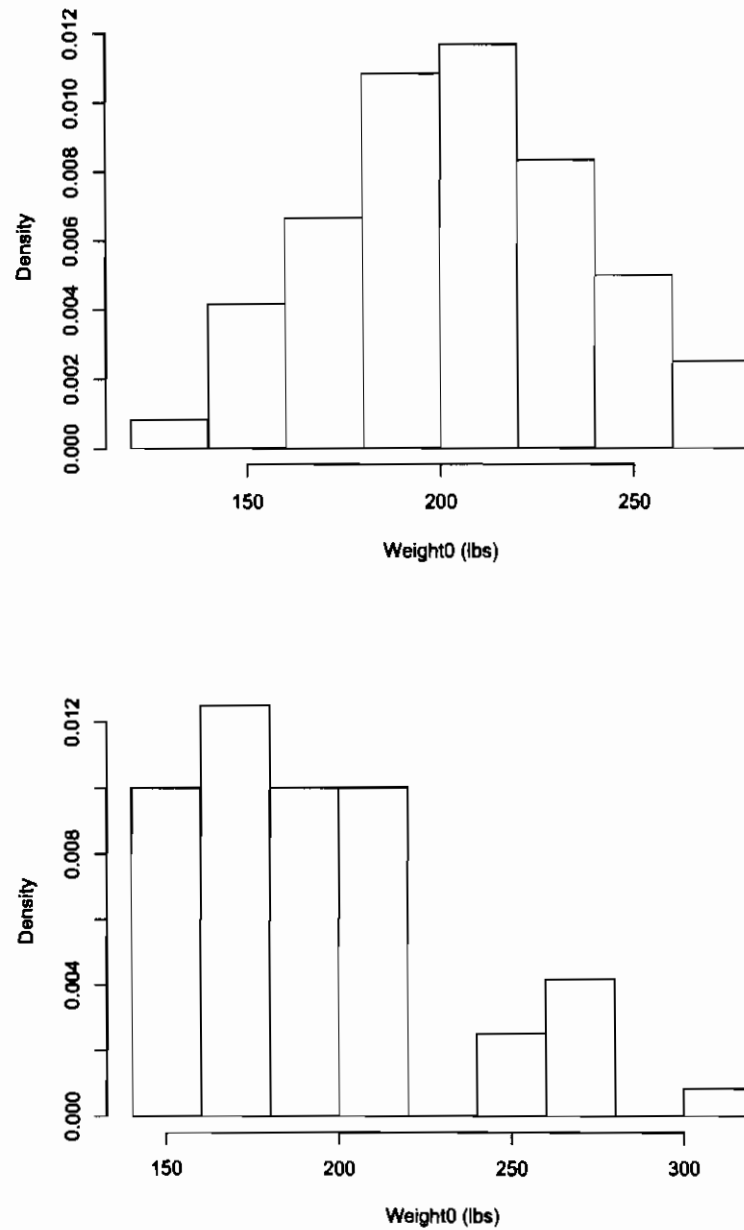


Figure 2: Histograms of weight at time 0 for the simulated data set (upper panel) and the Fleming data set (lower panel).

Appendix 1: R Functions Used in the Analysis of the Report.

1. Simulation of Values from a Multivariate Normal Distribution.

```
randdat<-function(muvect,Sigmat,n){  
  # requires package bayesurv  
  #  
  rawdat<-rMVNorm(n,muvect,Sigmat)  
  roundat<-round(rawdat,0)  
  orig<-1:60  
  ind1<-sample(orig,5)  
  ind2<-sample(orig[-ind1],9)  
  ind3<-sample(orig[-c(ind1,ind2)],4)  
  roundat[ind1,1]<-roundat[ind1,1]+0.25  
  roundat[ind2,1]<-roundat[ind2,1]+0.5  
  roundat[ind3,1]<-roundat[ind3,1]+0.75  
  ind11<-sample(orig,11)  
  roundat[ind11,2]<-roundat[ind11,2]+0.5  
  ind21<-sample(orig,9)  
  roundat[ind21,3]<-roundat[ind21,3]+0.5  
  ind31<-sample(orig,3)  
  roundat[ind31,4]<-roundat[ind31,4]+0.5  
  roundat<-cbind(1:n,roundat)  
  dat<-as.data.frame(roundat)  
  names(dat)<-c("subject","ht","wt0","wt1","wt2")  
  return(dat)  
}
```

2. Compare "suspect" data records to averages of other pairs.

```
checkavging<-function(dat,suspectno){
  suspect<-dat[dat$subject==suspectno,]
  rdat<-dat[-suspectno,]
  rn<-dim(rdat)[1]
  npairs<-rn*(rn-1)/2
  res<-c(rep(0,7))
  cnt1<-0
  repeat{
    cnt1<-cnt1+1
    t1<-rdat[cnt1,]
    cnt2<-cnt1
    repeat{
      cnt2<-cnt2+1
      t2<-rdat[cnt2,]
      tsubs<-c(rdat$subject[cnt1],rdat$subject[cnt2])
      #cat("tsubs: ",tsubs,fill=T)
      tavg<-0.5*(t1+t2)
      flag1<-(tavg$ht==suspect$ht)
      flag2<-(tavg$wt0==suspect$wt0)
      flag3<-(tavg$wt1==suspect$wt1)
      flag4<-(tavg$wt2==suspect$wt2)
      nflags<-flag1+flag2+flag3+flag4
      if(nflags>0){
        tres<-c(tsubs,nflags,flag1,flag2,flag3,flag4)
        res<-rbind(res,tres)}
      if(cnt2==rn) break
    }
  }
}
```



```
    }  
    if(cnt1==rn-1) break  
  }  
  return(res)  
}  
#-----  
summarycheckavg<-function(dat,suspectnos){  
  sk<-length(suspectnos)  
  res1<-NULL; res2<-NULL; res3<-NULL; res4<-NULL; res5<-NULL  
  res6<-NULL; res7<-NULL; res8<-NULL  
  cnt<-0  
  repeat{  
    cnt<-cnt+1  
    tsus<-suspectnos[cnt]  
    tres<-checkavg(dat,tsus)  
    rs<-dim(tres)[1]  
    if(is.null(rs)==FALSE){  
      if(rs==1){  
        res1<-c(res1,tsus)  
        res2<-c(res2,tres[1])  
        res3<-c(res3,tres[2])  
        res4<-c(res4,tres[3])  
        res5<-c(res5,tres[4])  
        res6<-c(res6,tres[5])  
        res7<-c(res7,tres[6])  
        res8<-c(res8,tres[7])  
      }  
    }  
  }  
}
```

```
if(rs>1){  
  cnt2<-0  
  repeat{  
    cnt2<-cnt2+1  
    ttres<-tres[cnt2,]  
    res1<-c(res1,tsus)  
    res2<-c(res2,ttres[1])  
    res3<-c(res3,ttres[2])  
    res4<-c(res4,ttres[3])  
    res5<-c(res5,ttres[4])  
    res6<-c(res6,ttres[5])  
    res7<-c(res7,ttres[6])  
    res8<-c(res8,ttres[7])  
    if(cnt2==rs) break  
  } } }  
if(cnt==sk) break  
}  
res<-data.frame(suspect=res1,other1=res2,other2=res3,nflags=res4,  
               flag1=res5,flag2=res6,flag3=res7,flag4=res8)  
res2<-res[res$other1!=0,]  
return(res2)  
}
```

3. Examine distributions of trailing digits.

```
digitdist<-function(dat){  
  ht<-dat$ht  
  wt0<-dat$wt0
```

```
wt1<-dat$wt1
wt2<-dat$wt2
ht<-floor(ht)
wt0<-floor(wt0)
wt1<-floor(wt1)
wt2<-floor(wt2)
ldht<-ht-10*floor(ht/10)
ldwt0<-wt0-10*floor(wt0/10)
ldwt1<-wt1-10*floor(wt1/10)
ldwt2<-wt2-10*floor(wt2/10)
htfs<-NULL; wt0fs<-NULL; wt1fs<-NULL; wt2fs<-NULL
cnt<--1
repeat{
  cnt<-cnt+1
  thtf<-sum(ldht==cnt)
  twt0f<-sum(ldwt0==cnt)
  twt1f<-sum(ldwt1==cnt)
  twt2f<-sum(ldwt2==cnt)
  htfs<-c(htfs,thtf)
  wt0fs<-c(wt0fs,twt0f)
  wt1fs<-c(wt1fs,twt1f)
  wt2fs<-c(wt2fs,twt2f)
  if(cnt==9) break
}
res1<-data.frame(digit=0:9,ht=htfs,wt0=wt0fs,wt1=wt1fs,wt2=wt2fs)
tstht<-sum((res1$ht-6)^2/6)
tstwt0<-sum((res1$wt0-6)^2/6)
```

```
tstwt1<-sum((res1$wt1-6)^2/6)
tstwt2<-sum((res1$wt2-6)^2/6)
pht<-1-pchisq(tstht,9)
pwt0<-1-pchisq(tstwt0,9)
pwt1<-1-pchisq(tstwt1,9)
pwt2<-1-pchisq(tstwt2,9)
res2<-data.frame(var=c("ht","wt0","wt1","wt2"),
                  tst=c(tstht,tstwt0,tstwt1,tstwt2),
                  pval=c(pht,pwt0,pwt1,pwt2))
res<-list(res1,res2)
return(res)
}
```

4. Compute influence values.

```
influencefctn<-function(dat){
  wt2<-dat$wt2
  wt1<-dat$wt1
  wtdif<-wt1-wt2
  mn<-mean(wtdif)
  v2<-var(wtdif)
  n<-length(wtdif)
  realt<-mn/sqrt(v2/n)
  subs<-NULL; infls<-NULL
  cnt<-0
  repeat{
    cnt<-cnt+1
    tsub<-dat$subject[cnt]
```

```
tvals<-wtdif[-cnt]
tt<-mean(tvals)/sqrt(var(tvals)/(n-1))
tinf1<-abs(tt-realt)
subs<-c(subs,tsub)
infls<-c(infls,tinf1)
if(cnt==n) break
}
res<-data.frame(subject=subs,influence=infls)
return(res)
}
```

Appendix 2: Data Sets Used in This Report.

1. The Fleming Data.

	subject	ht	wt0	wt1	wt2
1	63.5	164	160	157	
2	63.75	170	167	164	
3	62.75	178	176	176	
4	65	160	158.5	158	
5	65	149.5	145	139.5	
6	62.25	201.5	197.5	197.5	
7	70	214.5	212	211	
8	68.25	180	177	174	
9	64	180	177	175	
10	64.75	158.5	156.5	155	
11	67.25	176.5	173.5	173	
12	64	160	159	155	
13	65.5	220	213	211	

14 76 273 270 267
15 62 183.5 179 176
16 71 208 203.5 200
17 62.5 146 144 140
18 62.25 266.5 262 255
19 70 278.5 270.5 264
20 63.5 198.5 196.5 195
21 73.75 252 246 240
22 67.5 208 204.5 202
23 61.25 147.5 139 128.5
24 63 205 200 197
25 68 195 193 189
26 60.5 159 154 150
27 65 189 184 181
28 64.5 180 176 173
29 65 167 164 160
30 66 154 150 147
31 68 203 198.5 195
32 71 207 204 200
33 69 182 176 175
34 67.5 179 175 169
35 66.5 165.5 163 162
36 63 149 145 143
37 69 184 181 177
38 65 162 159 154
39 67 199 196 190
40 70 245 239 233

41 67 201 195 191
42 70 205 200 196
43 69 174 167 163
44 62.5 268 263 258
45 71 280 275 272
46 66 208 204 199
47 68 252 247 244
48 66 198 195 189
49 68 154 149 148
50 65 189 186 182
51 69 197 194 188
52 66 186 189 192
53 68 205 201 199
54 70 301 295 293
55 62 148 146 141
56 67 173 168 165
57 66 197 192 190
58 61 154 150 147
59 69 171 168 164
60 65 163 157 155

2. The Simulated Data.

subject	ht	wt0	wt1	wt2
1	67.5	207	202	200
2	62	161	161	161
3	70	269	263.5	254
4	65	188	184	181

5 69 249 244 237
6 67 166.5 162 157
7 75 211 208 204
8 66 208 205 202
9 65 205.5 200 196
10 66 206 200 197
11 65 181 178.5 174
12 66 200.5 196 192
13 66 171 168.5 167
14 71 235 232 231
15 66 179 173 170
16 61 161 157 155
17 63 179 175.5 174
18 72 147 145 143
19 70 231 225 220
20 63 136 132.5 125
21 63.25 217.5 213 212
22 69 236 231 226
23 67 171 166 162
24 71 193 188 186
25 67.5 174 169.5 166.5
26 72.5 265.5 258 254
27 65 214 211 207
28 65 185 180.5 180
29 63 192.5 189 184
30 67 231 227.5 224
31 65 192 188 185.5

32 67 218 217 216

33 63.5 184 177 168

34 65.75 222 215 209.5

35 67 207 201 196

36 66.5 257 256 254

37 72 223 218 212

38 71 221 214 210

39 66.25 213 209 206

40 66 239.5 236 233

41 67 143 140 137

42 64.25 221 216 211

43 66 209 203 198

44 68.25 181.5 179 177

45 69.5 243 234 229

46 70 252 247 242

47 64 158 156 155

48 68 222 220.5 215

49 70.5 257 249 242

50 69.75 219 216 212

51 69.25 156.5 154 150

52 68 191 187 184

53 64.5 182 180 174

54 73.75 252 247 242

55 70 194.5 190 186

56 61 210.5 206 204

57 68.5 265 257 253

58 62 187 182 177

40

59 71.75 198 192 188

60 64 145 142 140

Soy Chip Data: Examination for Anomalies

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1 Background

This report contains a statistical examination of data from a study titled "Efficacy of Soy Pasta Chips for Weight Loss", conducted in 2004 at the Flemming Heart and Health Institute of Omaha, Nebraska. My understanding is that questions have been raised about the authenticity of the data produced by that study and, specifically, whether some of those data may have been fabricated. Statistical examination of a set of data cannot "prove" or "disprove" falsification of data records, but it can determine whether certain types of anomalies exist that would not be expected in data from most scientific studies. The goal of this exercise was to uncover any such anomalies that might exist in the data from this study.

The data used in this analysis were taken from a final report signed by the principle investigator on 7 April 2004 and provided to me via electronic transmission by Dr. Richard Flemming. The data contain records for 60 individuals that consist of values for height, initial weight, weight at two weeks, weight at four weeks, and body mass index at the same time points as weight. My examination of these data makes use of only the directly recorded variables of height and the three weight measurements. Also provided was a set of data I was told were entirely fabricated by a Mr. Hansen and these data are examined in the same manner as for the Flemming data.

2 Methods of Examination

Appropriate statistical methods for examination of data to detect potential fabrication depend on the characteristics of the study or studies of concern, including study design, objectives, and the analysis used to reach conclusions. Also important is the type of data fabrication suspected. The best methods for detection of one or a few fabricated data records differ from those more appropriate for the

detection of wholesale fabrication of an entire or nearly an entire data set (e.g., Buyse *et al.* 1999). The study of concern here was of a very simple design with apparently self-selected subjects and lacking multiple medical centers or treatment groups, precluding the use of comparison of multiple centers or a suspect data set to an unsuspecting one (e.g., Al-Marzouki *et al.* 2009). The examination reported here focused on three aspects of the data records, *marginal and joint data structure*, *recorded data values*, and *influence on results*. The motivation for considering these aspects of the problem are described in this section.

Fabrication of data generally has a specific objective, either to influence the outcome of data analysis (e.g., show an effect of one or more treatments) or to avoid the effort needed to properly conduct data collection if a pattern seems clear from an analysis of some actual data. The former situation may result in alteration of one or more data records that have disproportionate influence on the outcome of statistical analysis for the study. Alternatively, if an entire data set is fabricated to exhibit an effect of some type (e.g., a difference in treatment group means), other characteristics of typical data sets that might also show such an effect (e.g., variance or covariance structure) are difficult to match. That is, most scientists cannot *preserve* higher-order structure in falsified data while achieving the desired first-order differences (Haldane 1948). The fabrication of data records as a matter of convenience may sometimes be detected based on either the number or distribution of digits in recorded data (e.g., Hill 2008, Walter and Richards 2001). For example, the presence of “extra” digits in recorded data may indicate that other, possibly legitimate, records have been averaged to produce the falsified data, or a fabricated data set may contain a preference for certain digits in either the first or terminal places. This latter phenomenon is related to the fact that the human mind is a poor random number generator.

While a comparable data set from an undisputed study is not readily available

for this analysis, it is possible to make use of theoretical probability distributions for comparison with the Flemming and Hansen data sets. Simulation of random values from theoretical probability distributions can be used to describe the expected behavior of actual data. Serious departures from such behavior are then a signal at something may be amiss in a given set of values. The Soy Chip study resulted in a four-dimensional multivariate observation for each subject, height, weight 0, weight 1, and weight 2. Assuming (which can be reasonably verified for the Flemming data) that a multivariate normal distribution provides a good model for the marginal and joint data characteristics, simulated values from this distribution can be used to examine what might be expected in terms of recorded data values (e.g., terminal digits) and whether or not averaging results should appear in randomly generated data.

3 Marginal and Joint Data Structure

The first approach used in this exercise was to examine the marginal and joint data structures for the entire set of data. This examination might indicate the presence of records that were altered in a manner that failed to preserve the overall coherence (or general behavior) of the collection of data in a manner consistent with typical probabilistic rules. For example, if a number of records were falsified for a particular weight (e.g., weight2 at week 4) they might stand out as having a different relation with height than they did at an earlier stage (e.g., weight1 at week 2). If entire data records were falsified the relation among variables in those records (ht, wt0, wt1, wt2) may not follow the overall pattern of the set of data. In a sense, then, this examination is one of *data consistency*. An individual falsifying a few data records would need to take care that those records “fit” the general pattern in the entire data set. An individual falsifying the bulk of records or fabricating an entire

data set would need to take care that those records were both biologically consistent and probabilistically consistent. Probabilistically consistent here means that there should exist some joint probability distribution that could have “generated” the observed data. While no theoretical probability distribution is “correct” in a real problem, real data tend to follow the patterns of data simulated from theoretical distributions and dictated by the rules of probability. Falsified data often fail to exhibit this same consistency (unless, of course, they were produced via simulation from theoretical probability distributions).

Basic summary statistics for the Flemming data set are presented in Table 1 and similar values for the Hansen data are presented in Table 2.

Variable	Min	Q1	Q2	Q3	Max	Mean	Variance
Height	60.50	63.94	66.00	68.44	76.00	66.32	10.439
Weight0	146.0	165.1	185.0	205.5	301.0	193.71	1409.587
Weight1	139.0	162.2	182.5	201.6	295.0	189.76	1370.250
Weight 2	128.5	159.5	179.0	199.0	293.0	186.41	1357.250

Table 1: Basic summary statistics for the Flemming data.

Variable	Min	Q1	Q2	Q3	Max	Mean	Variance
Height	60.00	64.38	69.00	71.00	75.00	68.02	18.334
Weight0	129.0	174.5	201.5	225.0	285.0	200.59	1398.563
Weight1	125.0	169.8	197.5	220.5	281.0	196.68	1380.898
Weight2	124.0	166.5	194.5	216.0	279.0	193.47	1403.165

Table 2: Basic summary statistics for the Hansen data.

The values in Table 1 and Table 2 are quite similar. The greatest difference in

summary statistics from these sets of values is that the range (maximum value minus minimum value) for weights in the Hansen data set are more constant than for the Flemming data set. These ranges are reported in Table 3. The greater consistency in range for the Hansen data may be indicative of a more systematic method of data production, but without the knowledge that these data are purportedly fabricated it would be difficult to reach that conclusion on the basis of the ranges given in Table 3.

Data Set	Range for Variable			
	Height	Weight0	Weight1	Weight2
Flemming	15.5	155.0	156.0	164.5
Hansen	15.0	156.0	156.0	155.0

Table 3: Ranges for the Flemming and Hansen data sets.

Correlations among the variables of height, weight0, weight1 and weight2 are reported for the Flemming data in Table 4 and the Hansen data in Table 5. Again, these values are quite similar, actually remarkably so. There is little to suggest that either set of data are not internally consistent. Extremely high correlations (for which the values of correlations between weight0, weight1 and weight 2 would qualify) are sometimes taken as an indication of results “too good to be true” (e.g., Akhtar-Danesh and Dehghan-Kooshkghazi 2003). But that is a weak argument against either the Flemming or Hansen data sets in this case. The reason is a combination of the ranges for weight measurements in Table 3 and the physiological realities of how much weight an individual can gain or loose in a period of several weeks. Correlation is a measure of linear association between two variables and this measure is affected by the range of values considered. A wide range of initial values (e.g., a range of 155 lbs. in weight0 for comparison with weight1 or a range of 156 lbs in weight1 for a comparison with weight2), coupled with the biological reality that

any individual is unlikely to loose or gain more than a small fraction of their initial value *relative to the initial range* indicates that high correlations are to be expected in this situation. Both the Flemming and the Hansen data are also consistent with the anticipation that weights observed at more distant time points (i.e., weight0 and weight2) should be less highly correlated than weights observed at less distant time points (i.e., weight0 and weight1).

	ht	wt0	wt1	wt2
ht	1.0000000	0.5263469	0.5274059	0.5289093
wt0	0.5263469	1.0000000	0.9989028	0.9961254
wt1	0.5274059	0.9989028	1.0000000	0.9983947
wt2	0.5289093	0.9961254	0.9983947	1.0000000

Table 4: Correlations for the Flemming data.

	ht	wt0	wt1	wt2
ht	1.0000000	0.5891542	0.5936949	0.5839262
wt0	0.5891542	1.0000000	0.9990095	0.9965339
wt1	0.5936949	0.9990095	1.0000000	0.9985730
wt2	0.5839262	0.9965339	0.9985730	1.0000000

Table 5: Correlations for the Hansen data.

One caution is in order here concerning the marginal distributions of the variables height and initial weight (i.e., weight0). It may be tempting to compare the empirical distributions (as histograms, for example) of these variables in a given set of data to what is known about values for the national population as a whole. For example, if one looks at the distribution of weights for the population of males and

females at large, one should anticipate seeing a bimodal distribution. In a study of 60 individuals chosen randomly from the overall population one might anticipate a similar distribution for observed values in the sample. However, in a set of 60 self-selected individuals, such as in the current situation, one **may not** anticipate that the empirical distribution of the sample will appear closely similar to the population distribution. The distribution of heights or initial weights in a self-selected sample from any population are just as likely to look dissimilar to the population distributions as they are to look similar to the population distributions. Histograms of height values for the Flemming and Hansen data are presented in Figure 1. Here, the distribution of heights from the Hansen data appears to have an excess of tall individuals, which would not be expected if the data corresponded to a random sample of the population of individuals in the United States. However, given that the values would not correspond to a random sample of individuals in the population, it would be misleading to claim that the empirical distribution in the lower panel of Figure 1 provides evidence of falsified data.

Scatterplots of weights at times 0, 1 and 2 against height are presented for the Flemming data in Figure 2 and for the Hansen data in Figure 3. The first thing to note here is the similarity of the three scatterplots for each set of data. This should be expected, again because of the total range of weights contained in the data sets and the physiological realities of how much weight can change for humans over a period of several weeks. It appears that one could pick out individuals on these plots and that is, in fact, true. What would be disturbing would be to find individuals with radically different positions on one or more of the three plots and that does not occur. One may also notice that there are more widely scattered points above the bulk of the data pattern than there are below, for both data sets. This is not necessarily to be unexpected, at least in the Flemming data, because the self-selected sample of participants were individuals who considered themselves overweight. Statistically,

this data pattern suggests distributions of weight for given heights that are skew right rather than symmetric. That this same pattern is exhibited in the Hansen data suggests that the fabrication of the Hansen data set was undertaken in a way to preserve features of the Flemming data.

Overall, there is little in either of the sets of values examined to suggest that they could not be the result of studies with an absence of fabricated data. Both sets of values may be considered as *internally consistent*. At this point we would have no justification for suggesting that either set of data have been manipulated in a manner consistent with the falsification of data. Examination of data sets in the manner of this section is not a powerful approach for identification of anomalies for this situation because of the lack of a reference for comparison. The population as a whole will not serve this purpose because subjects in the Flemming study were not intended to be a random sample from the population, and we lack data from a comparable undisputed study for comparison as well. What we can say is that neither data set contains obvious glaring inconsistencies that would suggest fabrication of data.

4 Recorded Data Values

Any numerical data value consists of a sequence of digits. For example, the value of 156 for an initial weight in this study has the digits 1, 5 and 6, in that order. There are two common approaches for examination of recorded digits in data records – investigation of recorded values that contain “extra digits”, and comparison of distributions of the values 0 through 9 in various places in the data (e.g., first digit or last digit). We consider these two approaches in turn.

4.1 Records with Extra Digits

The majority of the data contained in the Flemming data set are recorded to the nearest whole number (e.g., height to the nearest inch, weight to the nearest pound) but there are a number of records that contain extra digits of either 0.25, 0.5 or 0.75. Table 6 presents the frequencies of these extra digits for the four observed variables.

Extra Digits	Height	Weight0	Weight1	Weight2
0.25	5	0	0	0
0.50	9	11	9	3
0.75	4	0	0	0

Table 6: Frequency of extra digits in the Flemming data.

Data records with extra digits relative may indicate that other data records were averaged to produce the suspect record (e.g., Walter and Richards 2001). For example, if two records with weights of 174 and 177 are averaged the result is 175.5, and the extra digit is easily recorded by an individual falsifying data. Of course, the mere presence of extra digits in some records does not necessarily indicate the record was constructed, but in the absence of falsification it would be unusual for one (entire) record to be the average of two others, even more unusual for this to be true of two records, and so forth. In the Flemming (and Hansen) data there are four variables, giving rise to four possible places where data averaging may have occurred to produce false data. A computer function was written (see Appendix 1) which took each record with extra digits for height and compared values of the four variables to averages of all other unique pairs of records (of which there are $59(58)/2 = 1711$). Each instance in which any of the variables in the “suspect” record with extra digits was found to correspond to the average of two other records

was saved. Of the 18 suspect records in the Flemming data, pairs of other subjects were found such that the average of exactly one variable in those records matched the value in the suspect record in 17 cases. For 12 of the suspect records pairs of other subjects could be found that, when averaged, produced the values in the suspect record for exactly 2 variables. But for none of the suspect records was it possible to locate a pair of other subjects that when averaged produced 3 or all 4 of the variables in the suspect record. The results for suspect records having at least two variables equal to the average of other records are presented in Table 7. In this table, the column labeled "suspect" gives the subject number from the original data corresponding to a data record having extra digits for height. The columns labeled "other 1" and "other 2" give subject numbers from two other records that were found to average to the suspect record value for two or more of the variables. The column labeled "nflags" gives the number of variables (out of the 4 possible but at least 2) for which the two other records produced averages equal to what was reported for the suspect record, and the columns labeled "flag1" through "flag4" give the specific variables for which averages matched the value of the suspect record (flag1=height, flag2=weight0, flag3=weight1 and flag4=weight2).

There are several aspects of the results in Table 7 that are of interest.

1. Note first that there are quite a few of the records with extra digits for height (12 out of 18 to be exact) that have at least two variables equal to the averages of two other records in the data set.
2. Curiously, many of the suspect records in Table 7 contain variables that have values equal to the average of more than one pair of other records (e.g., suspect record 1, 2, 6, 8).
3. The number of suspect records that have values equal to averages of other records seems more prevalent for weight variables than for the variable of

suspect	other1	other2	nflags	flag1	flag2	flag3	flag4
1	17	28	2	1	0	1	0
1	17	33	2	0	1	1	0
1	28	55	2	0	1	0	1
1	34	36	2	0	1	1	0
2	12	28	2	0	1	0	1
2	27	30	2	0	0	1	1
2	27	58	2	0	0	1	1
6	24	48	2	0	1	1	0
6	42	48	2	0	1	1	0
8	6	10	2	0	1	1	0
8	9	28	2	0	1	0	1
8	38	48	2	0	1	1	0
8	50	59	2	0	1	1	0
10	34	55	2	1	0	0	1
11	53	55	2	0	1	1	0
13	25	40	2	0	1	0	1
22	44	55	2	0	1	1	0
26	17	29	2	0	0	1	1
28	3	33	2	0	1	1	0
28	27	56	2	0	0	1	1
28	27	59	2	0	1	1	0
28	41	60	2	0	0	1	1
28	50	59	2	0	1	0	1
28	53	58	2	1	0	0	1
34	25	60	2	0	1	1	0
34	26	39	2	0	1	1	0
34	39	49	2	1	0	0	1
35	12	43	2	1	0	1	0
35	12	59	2	1	1	0	0

height.

4. There are no suspect records that are the same in total (i.e., for all four variables) to averages of other records. In fact, there does not appear to be a simple pattern for which variables are averages of other records. For example, subject numbers 17 and 28 as well as subject numbers 17 and 33 average to the value of weight1 for subject number 1. Subject numbers 17 and 28 also average to the height value for subject 1, but subject numbers 17 and 33 do not, while subject numbers 17 and 33 average to the value of weight0 for subject 1 but subject numbers 17 and 28 do not.

Overall, the results of Table 7 indicate that, if the suspect records with extra digits for height in the Flemming data were constructed using a process of averaging other data records, this was done according to some complex system that is difficult to uncover. For example, subject 1 had matches (i.e., flags) that involved subject numbers 17, 28, 33, 55, 34 and 36. The record for subject 1 was not a match for the average of any 3 of these other records (of which there are 20), any 4 of these records (of which there are 15), any 5 of these records (of which there are 6) or all 6 of the records. The number of instances in which some variables in the records for which height contained extra digits turn out to be equal to averages of other records is, however, curious.

To examine whether or not the phenomena of Table 7 should be considered "out of the ordinary", I compared the results given in that table with data generated randomly from a coherent probabilistic structure. To accomplish this, 60 records were simulated from a four-dimensional multivariate normal distribution with means, variances, and covariances equal to the realized values from the Flemming data set. This data set, then, was simulated to match the marginal and joint data structures of the Flemming data set, but to be a case in which other aspects of the data followed a typical probabilistic structure difficult for humans to duplicate

if asked to purposely falsify data (this entire simulated data set is contained in Appendix 2). The four variables in the simulated data will be called height, weight0, weight1 and weight2, in analogy with the actual problem. Each simulated record was then rounded to the nearest whole number. Following the frequencies of Table 6, 18 values for the variable height were randomly selected to have an extra digit added to their values; to 5 records the value of 0.25 was added, to 9 records the value of 0.50 was added, and to 4 records the value of 0.75 was added. In addition, 11 records were randomly selected to have a value of 0.50 added to weight0, another 9 records randomly selected to have a value of 0.50 added to weight1, and 3 records were randomly selected to have a value of 0.50 added to weight2. Running these simulated data through the same computer function used to produce Table 7 from the Flemming data gave the results presented in Table 8.

Although there is a minor difference between the values of Table 8 and those from the Flemming data of Table 7 (i.e., 7 of the 18 "suspect" records in the simulated data matched averages of other records in 2 or more variables, while 12 of 18 did for the Flemming data) the patterns are remarkably similar. In fact, the second, third, and fourth characteristics of the data in Table 7 listed previously, which may have seemed suspicious, were reproduced nearly identically in the simulated data results of Table 8.

Neither Table 7 nor Table 8 report the number of "suspicious" records matching averages in only 1 of the four variables. A table of frequencies for the number of suspicious records (out of 18 for both the Flemming and simulated data) that had 1, 2, 3, or 4 of the variables height, weight0, weight1, and weight2 matching averages of pairs of other data records is presented in Table 9. An ordinary Chi-squared test of differences for these frequencies is not appropriate here as the entries in Table 9 are not independent (i.e., a given suspicious data record could have matches with multiple pairs of other records, some pairs matching 1 of the variables and

suspect	other1	other2	nflags	flag1	flag2	flag3	flag4
25	16	58	2	0	1	1	0
33	11	58	2	1	1	0	0
34	15	57	2	0	1	1	0
34	17	57	2	1	1	0	0
34	49	58	2	0	1	0	1
39	1	50	3	0	1	1	1
39	2	57	2	0	1	1	0
39	32	35	2	0	0	1	1
42	5	24	2	0	1	1	0
42	22	35	2	0	0	1	1
42	28	49	2	0	1	0	1
42	37	38	2	0	0	1	1
50	1	30	2	0	1	0	1
59	25	34	2	0	1	0	1

Table 8: Data records in a simulated data set with heights recorded with extra digits for which variables were found to equal averages from two other records.

other pairs matching 2 of the four variables). In addition, only one simulated data set is presented and other simulated data sets would vary from this one to some degree. The point of Table 9, however, is that it does not appear that the Flemming data are at all unusual compared to what might result from a completely random probabilistic mechanism with the same marginal and joint data characteristics. The only conclusion that seems plausible is that the patterns exhibited in the Flemming data and reported in Table 7 are entirely in concert with what might occur from a completely probabilistic structure matched to the marginal and joint structures of those data.

Data Set	No. of Variables			
	1	2	3	4
Flemming	17	12	0	0
Simulated	14	7	1	0
Hansen	7	4	0	0

Table 9: Frequency of matches for “suspicious” data records with averages of other pairs of records for the Flemming, Hansen, and simulated data sets.

It may also be of interest to examine the purportedly falsified Hansen data in the same manner as presented in Table 7 for the Flemming data and Table 8 for the simulated data. In these data, 7 records for “height” contain an extra digit of 0.50. Of these 7 records all 7 matched averages of other pairs of data records for 1 of the four variables, and 4 matched averages for 2 of the four variables, as indicated in the final row of Table 9. Thus, the Hansen data seem to follow the same pattern exhibited by both the Flemming and simulated data. It is not clear what exactly should be made of this, other than that the Hansen data appear to have much the same behavior as the Flemming data with regard to averaging, and both have behavior similar to randomly simulated data as well.

4.2 Distributions of Digits

There exist demonstrated distributions for the frequencies with which different digits (0 through 9) appear in data from various sources. None of these is applicable to the current situation, and this subsection is included to indicate why this is so. There is a result known as *Benford's law* that indicates the relative frequencies of leading digits in data should follow an approximate logarithmic distribution (e.g., Buyse *et al.* 1999, Hill 2008). This approximation often applies to financial data and other data consisting of an aggregation of various sources but does not typically apply to scientific data from a single data source (e.g., Hill 2008). In fact, a proof that Benford's law corresponds to a coherent probabilistic structure made use of random digits selected from random distributions (Hill 1996), a context that does not apply to most scientific investigations. The emphasis put on Benford's law by, for example, Buyse *et al.* 1999 seems misplaced, except perhaps in the examination of financial records for medical facilities.

The other use of distributions of digits in data to detect anomalies rest on the assumption that recorded data values may contain meaningful and nonmeaningful digits. The leading (first) digits of data values are often meaningful in indicating the magnitude of responses. The trailing (last) digit or digits are often nonmeaningful in this regard. For example, in a weight difference of 190.3 and 185.6 pounds, the first three digits of 190 and 185 are more meaningful than are the trailing decimal digits of 3 and 6. It is often assumed then that the meaningless digits should follow a uniform distribution on the discrete integer values from 0 to 9. Because the human mind appears to be a poor random number generator, fabricated data may often show a distribution of meaningless digits substantially different from a uniform distribution (e.g., Walter and Richards 2001). But, as pointed out by O'Kelly (2004), data with non-meaningful trailing digits are relatively unusual in most clinical trials, and that is the case here except for perhaps the data records with extra recorded digits, which

have already been examined in the previous subsection.

Nevertheless, in order to demonstrate what an examination of trailing digits would suggest about the three data sets currently under investigation (the Flemming data, the Hansen data, and the simulated data) I wrote a computer function to give the frequency of final digits (as whole numbers – data records containing extra digits first had those digits removed) for each of the variables of height, weight0, weight1, and weight2, and to test the resultant empirical distributions against a theoretical uniform distribution. The results for the Flemming data are presented in Tables 10 and 11.

Digit	ht	wt0	wt1	wt2
0	6	8	7	8
1	5	4	2	5
2	7	4	3	5
3	6	5	6	6
4	4	7	8	6
5	8	6	7	9
6	7	4	9	3
7	6	5	7	7
8	6	10	4	5
9	5	7	7	6

Table 10: Observed frequencies of final digits in the Flemming data.

Under an assumption that the relative frequencies of final digits (0 through 9) should follow a uniform distribution, the expected frequency for each digit is, with 60 observations $60/10 = 6.0$. Standard Chi-squared tests of goodness of fit for such a uniform distribution to the values in Table 10 yields the results of Table 11. Clearly, none of the variables contain distributions of final digits coming even close to having

evidence of departure from a uniform distribution.

Variable	Test Statistic	<i>p</i> -value
Height	2.00	0.9915
Weight0	6.00	0.7399
Weight1	7.67	0.5680
Weight2	4.33	0.8881

Table 11: Test statistics and associated *p*-values for testing that the frequencies of final digits in the Flemming data differ from a uniform distribution.

Repeating this exercise with the data simulated from a multivariate normal distribution yields the observed frequencies of Table 12 and the associated test statistics and *p*-values of Table 13. These simulated data, as they should, also offer no evidence of a departure from a uniform distribution of final digits for any of the four variables.

Finally, conducting the procedure once again for the Hansen data produces the observed frequencies of Table 14 and the associated test statistics and *p*-values of Table 15. In this case, it would appear that the final digits of 0 and 5 appear with sufficiently greater frequency than expected (in combination – neither frequency would be sufficient by itself) than other digits to result in evidence that for the variable of weight0 that final digits differ substantially from what would be expected under a uniform distribution. Whether this is, or is not, truly meaningful could be a matter of debate. No such evidence is present for the other three variables of height, weight1 or weight2. While this is certainly a curious feature of the Hansen data, I would be reluctant to attach too much meaning to this result if I had not been informed that the Hansen data were fabricated. This one lone test statistic, in the face of internal consistency as demonstrated in Section 3 and consistency with the averaging property of Section 4, would seem scant evidence on which to base a

Digit	ht	wt0	wt1	wt2
0	5	2	7	7
1	6	12	4	4
2	5	7	7	9
3	6	5	4	3
4	4	4	5	11
5	8	6	5	5
6	9	5	8	8
7	8	7	8	8
8	4	5	7	3
9	5	7	5	2

Table 12: Observed frequencies of final digits in the simulated data.

Variable	Test Statistic	<i>p</i> -value
Height	4.67	0.8623
Weight0	10.33	0.3242
Weight1	3.67	0.9320
Weight2	13.67	0.1345

Table 13: Test statistics and associated *p*-values for testing that the frequencies of final digits in the simulated data differ from a uniform distribution.

declaration of falsification. While certainly curious as compared to the results for the Flemming and simulated data sets, it seems one would need to be “reaching for straws” to conclude that this offers real evidence that the Hansen data have been falsified.

The upshot of this subsection is that, in the first place, the examination of any

Digit	ht	wt0	wt1	wt2
0	9	13	4	9
1	7	2	4	8
2	9	4	7	8
3	6	10	7	7
4	7	2	6	3
5	6	13	10	6
6	3	1	5	4
7	2	6	5	2
8	4	7	5	6
9	7	2	7	7

Table 14: Observed frequencies of final digits in the Hansen data.

Variable	Test Statistic	p -value
Height	8.33	0.5009
Weight0	32.00	0.0002
Weight1	5.00	0.8343
Weight2	8.00	0.5341

Table 15: Test statistics and associated p -values for testing that the frequencies of final digits in the Hansen data differ from a uniform distribution.

of the data sets (Flemming, Hansen, or simulated) for assumed distributions of digit values in either leading or trailing places could prove problematic on theoretical grounds. There is no solid reason to assume that any of these data sets (aside from the simulated data) should exhibit any particular distribution of digits in any order, other perhaps than that weights should not have leading digits less than 1

for overweight individuals (i.e., less than 100 pounds) and would be unlikely to have leading digits greater than 3, even for a sample of offensive linemen from the national football league. That the trailing digits of the Hansen data set appear to have some departure from a hypothesized uniform distribution for the variable `weight0` certainly is of interest, but also is certainly not definitive in offering evidence of falsification.

5 Could the Flemming Data Be Simulated?

The agreement of the Flemming data with values simulated from a multivariate normal distribution in terms of the averaging phenomena discussed in section 4.1, and the distribution of trailing digits in Section 4.2, raises the question of whether the data could have been produced wholesale (i.e., in entirety) from the use of a random number generator. The most likely candidate for such simulation would be a multivariate normal distribution with marginal and joint characteristics equal to the means, variances, and covariances reported for the Flemming data and described in Section 3 of this report. Given a moderate amount of statistical sophistication, anyone could produce such a data set. That this is unlikely to be the case in the current situation is evidenced by the failure of marginal distributions of `weight0`, `weight1`, and `weight2` to follow univariate normal distributions. A known property of multivariate normal distributions is that the marginal distributions corresponding to individual variables are univariate normal in form. Figure 4 presents histograms of the marginal distributions of `weight0` for the simulated data set in the upper panel and the Flemming data set in the lower panel. The simulated data (upper panel) exhibit a distribution consistent with a normal theoretical distribution, which they should. The Flemming data (lower panel) exhibit a distinct skew right distribution, consistent with the observation of the scatterplots of weight versus height in Figure

2 (see Section 3 of this report). Is it possible to simulate data that have the characteristics of the Flemming data set? The answer is yes, it is possible, but doing so would require the ability to preserve means, variances, and correlations as described in Section 3 of this report, preserve the averaging property described in Section 4 of this report, **and** produce the difference in marginal distribution of weights at time 0 given in Figure 4. There exist ways to achieve all of this but they require a relatively high level of statistical knowledge, including the time and ability to write computer functions for tasks that are not readily available in pre-packaged routines.

6 Influence on Results

Falsification of data often has the objective of producing certain results in a data analysis. Quantification of the *influence* of each observation on the resultant analysis can then sometimes highlight one or a group of observations that played a large role in determining the outcome and conclusions of a study. While not in any manner evidence of falsified values by themselves, the occurrence of high influences can suggest cases worthy of additional examination. In the report on results of the Flemming study provided to me, the analysis consisted of two paired t-tests, one conducted on the difference in weight0 and weight1 values and the other conducted on the differences in weight1 and weight2 values. To examine the influence of recorded data values on these tests I simply deleted observations one at a time from the data, recomputed the test statistic without that value, and took the difference (absolute value) of that deleted-case statistic with the test statistic computed using the entire data set. This value then provides an indication of the influence of individual observations on the test conducted with the entire set of values. A summary of the influence values produced using the Flemming, Hansen, and simulated data for the comparison of weight0 and weight1 values is presented in Table 16, and the same is

reported for the comparison of weight1 and weight2 values in Table 17.

Data Set	Min	Q1	Q2	Q3	Max
Flemming	0.0223	0.1758	0.2461	0.3079	2.8390
Hansen	0.0042	0.1883	0.3102	0.3133	2.4840
Simulated	0.0211	0.1309	0.2784	0.3265	0.9403

Table 16: Summary of influence values for comparison of weight0 and weight1 records.

Data Set	Min	Q1	Q2	Q3	Max
Flemming	0.0111	0.1564	0.1833	0.2376	1.306
Hansen	0.0631	0.1347	0.1928	0.2400	0.9118
Simulated	0.062	0.1794	0.2491	0.2818	0.5538

Table 17: Summary of influence values for comparison of weight1 and weight2 records.

The most notable feature of both Table 16 and Table 17 is the extreme distance between the third quartile (or 75%-tile, denoted Q3) of influence values and the maximum influence value for the Flemming data in both Table 16 and Table 17, and the Hansen data, at least in Table 16. Stem and leaf plots demonstrate that this is due to only one extreme value that is hugely separated from the remainder of the data. For example, the influence values for the Flemming data of Table 16 have the following stem-and-leaf plot:

The data record that corresponds to the single observation with influence value 8 (which is just over 9 times larger than the next largest value) corresponds to subject 52 having height= 66, weight0= 186, weight1= 189 and weight2= 192. This subject gained weight between each weighing. The result is that, while highly influential relative to any of the other data records, the results for this subject decreased the size of the test statistic and hence the significance of the overall findings of the study. If this record was falsified the only reasonable objective would have been to purposely introduce one outlier into the data to make it look more "real", not to produce a desired result in the analysis of the study. This same observation is also the one extreme influence value for the Flemming data from Table 17.

Curiously, the Hansen data also contain exactly one such record, for what would be subject 45 in those data, with values height= 72, weight0= 275, weight1= 277 and weight2= 279. I surmise at this point that the Hansen data were not fabricated from scratch but, rather, took the Flemming data as a template to which various modifications were made in a haphazard but more-or-less “symmetric” manner. This would explain the close correspondence between marginal and joint data distributions for the Flemming and Hansen data and the reason the Hansen data

appear internally consistent (see Section 3). If those modifications were made haphazardly (i.e., by simply switching records and writing down different trailing digits in a seemingly haphazard manner) then this would also explain the trailing digit preference for weight0 seen in the Hansen data although, again, I hesitate to make too much of this occurrence.

7 Conclusions

As stated in the opening paragraph of this report, a statistical examination of data cannot definitively prove or disprove the falsification of data records. The analysis conducted in this report, however, does allow the following conclusions to be comfortably reached.

1. If the Flemming data were falsified it would appear that they were fabricated in a nearly wholesale fashion, that is, more-or-less in total. These data are internally consistent, consistent with the behavior of values simulated from a theoretical probability distribution, and there is only one data record with undue influence on the results of the study (and this influence was in the "wrong" direction).
2. Because of the properties listed in conclusion 1 and, in particular, the averaging behavior described in Section 4 that the Flemming data shared with simulated data, the most likely mechanism for fabrication in this study must be considered simulation from some theoretical probability model.
3. Because of the multivariate nature of the four recorded data values for each subject, maintaining internal consistency would require, or at least strongly suggest, that a multivariate probability distribution would need to have been employed to simulate data values. The candidate most readily available to

non-statisticians (and even to statisticians without extensive experience in the construction of multivariate distributions from other probability structures) is the multivariate normal distribution.

4. The marginal moments (means, variances) and joint moments (covariance or correlation) of the Flemming data could easily be maintained through simulation from a multivariate normal distribution. However, the skew shape of marginal weight distributions (e.g., Figure 4) could not.
5. Combining items 1 through 4 immediately above suggests that, if the Flemming data were fabricated, the procedure used to arrive at the reported values was necessarily complex, requiring considerable statistical expertise and time to conduct. If it were supposed that the most likely motivation for data fabrication in this situation was to save time and effort relative to actually performing the observational process, this would seem at odds with what would have been needed for fabrication of the data.
6. Finally, the Hansen data represent an interesting construction if they were produced from scratch, but much less so if they were produced through modification of the Flemming data. If they were produced from scratch they achieved remarkable success in preserving marginal and joint data structure and relative evenness in influence (either through chance or design). If they were produced through modification of the Flemming they simply borrowed these properties from values that already possessed them. My suspicion is that these values were obtained by either modifying the Flemming data or, at the very least, using those data as a template for construction. The one property expected of actual data that could not be entirely maintained in the Hansen data was a uniform distribution of trailing digits in recorded values, although whether this is a valid criterion for the current situation is not entirely clear,

as explained in Section 4.2.

Overall, there is simply no data-driven evidence that the Flemming data set is other than would be expected under a legitimate study. While there are several aspects of the Hansen data set that might cause concern, there is no definitive indication that these data were fabricated either, absent the knowledge that this was the case. This would not be unexpected if the Hansen data were patterned after the Flemming data, but if the Hansen data were fabricated from scratch they should be preserved as a case study against which to test statistical methods of unusual patterns in falsified data.

8 Literature Cited

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Figures

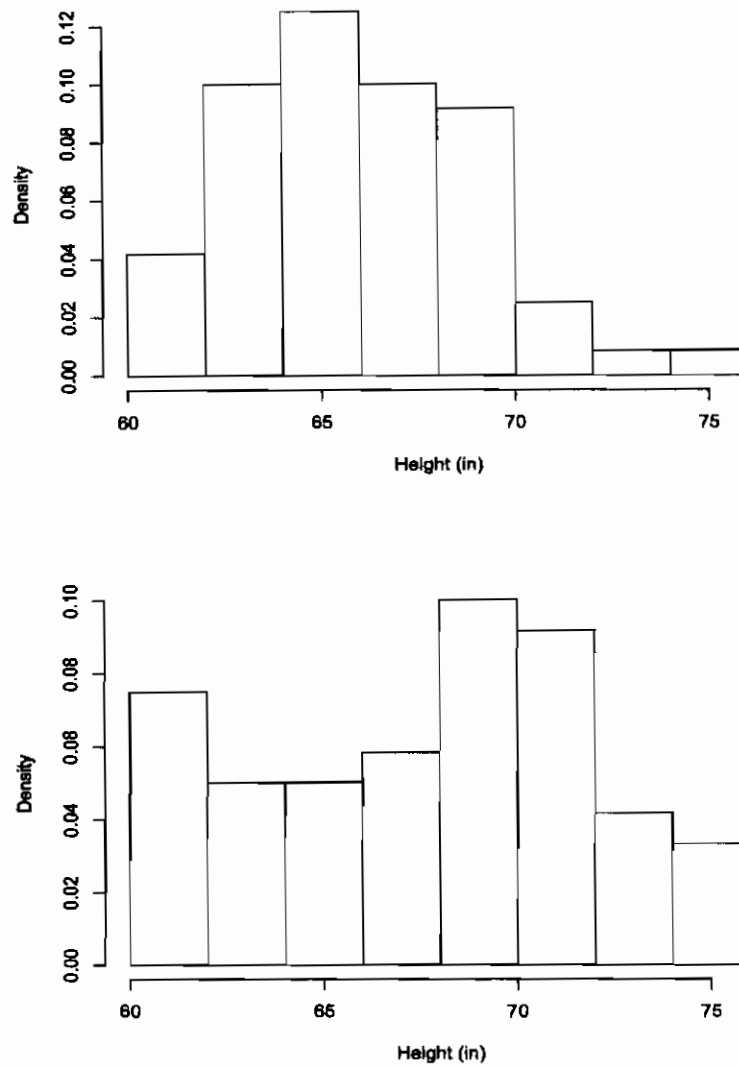


Figure 1: Histograms of height values from the Fleming data (top) and Hansen data (bottom).

30

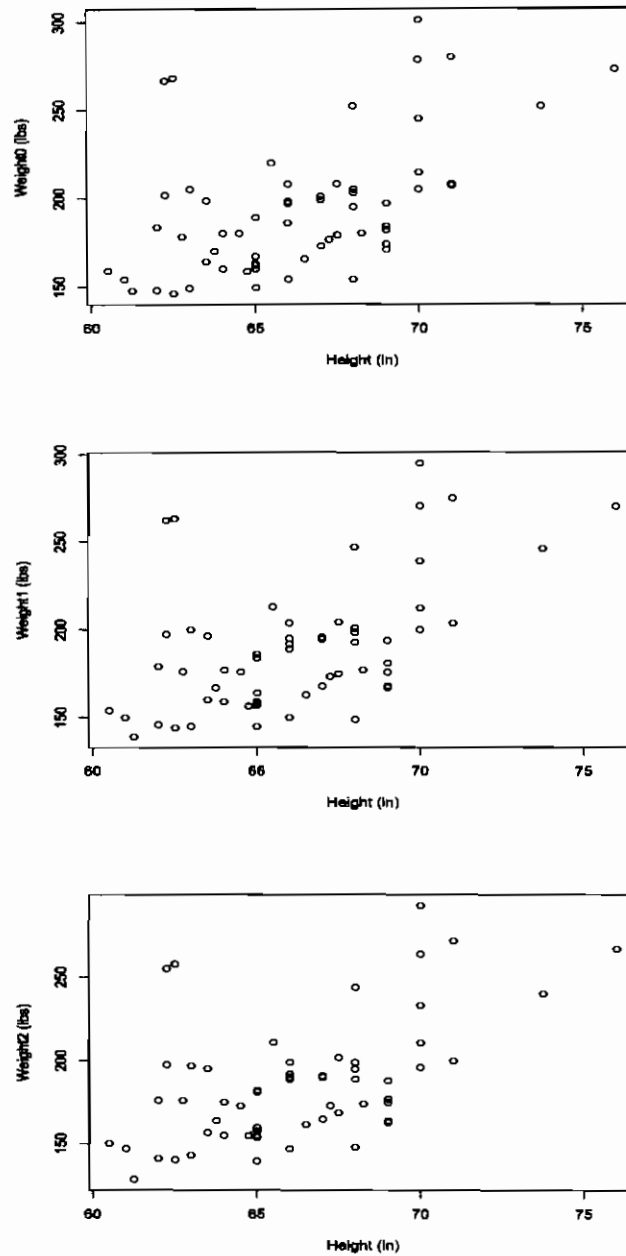


Figure 2: Scatterplots of weights against heights for the Flemming data.

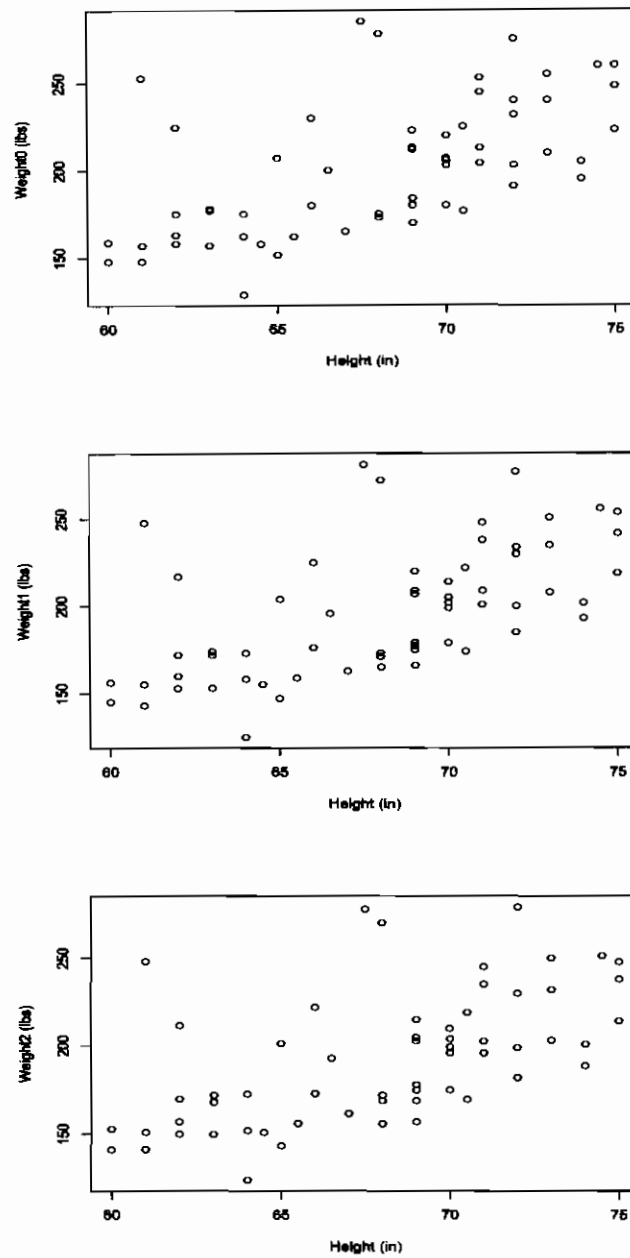


Figure 3: Scatterplots of weights against heights for the Hansen data.

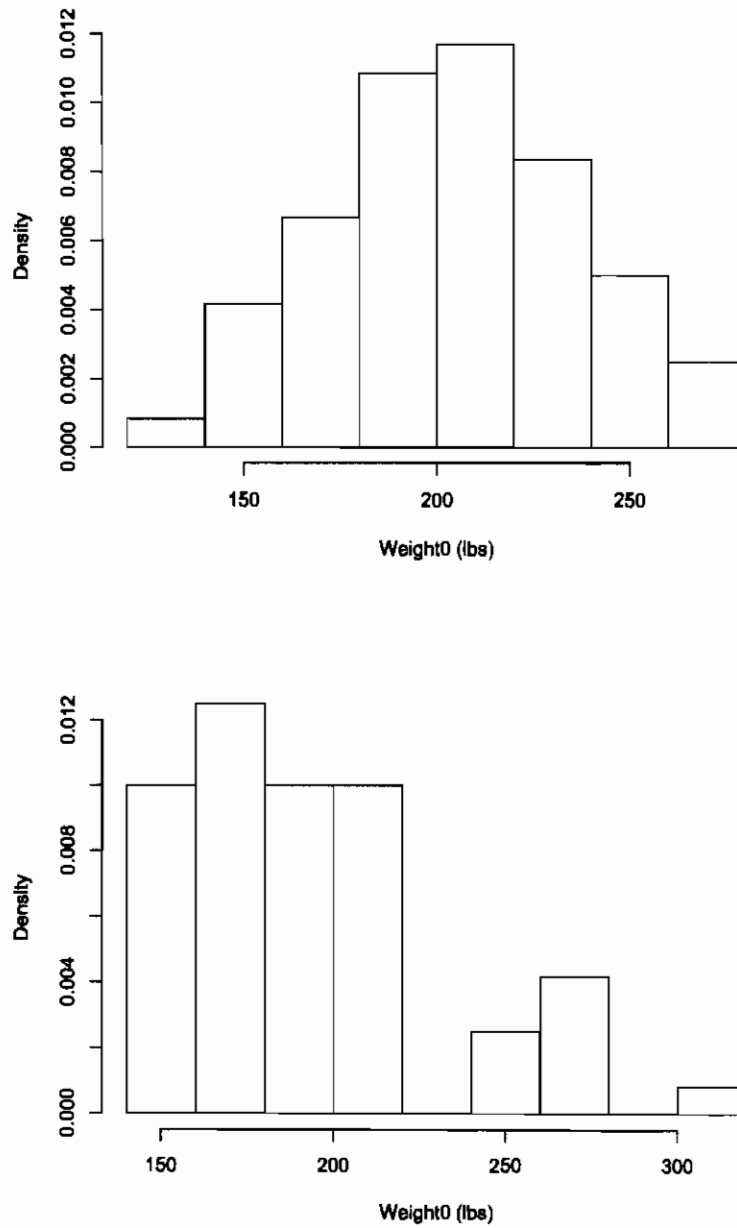


Figure 4: Histograms of weight at time 0 for the simulated data set (upper panel) and the Fleming data set (lower panel).

Appendix 1: R Functions Used in the Analysis of the Report.

1. Simulation of Values from a Multivariate Normal Distribution.

```
randdat<-function(muvect,Sigmat,n){  
  # requires package bayesurv  
  #  
  rawdat<-rMVNorm(n,muvect,Sigmat)  
  roundat<-round(rawdat,0)  
  orig<-1:60  
  ind1<-sample(orig,5)  
  ind2<-sample(orig[-ind1],9)  
  ind3<-sample(orig[-c(ind1,ind2)],4)  
  roundat[ind1,1]<-roundat[ind1,1]+0.25  
  roundat[ind2,1]<-roundat[ind2,1]+0.5  
  roundat[ind3,1]<-roundat[ind3,1]+0.75  
  ind11<-sample(orig,11)  
  roundat[ind11,2]<-roundat[ind11,2]+0.5  
  ind21<-sample(orig,9)  
  roundat[ind21,3]<-roundat[ind21,3]+0.5  
  ind31<-sample(orig,3)  
  roundat[ind31,4]<-roundat[ind31,4]+0.5  
  roundat<-cbind(1:n,roundat)  
  dat<-as.data.frame(roundat)  
  names(dat)<-c("subject","ht","wt0","wt1","wt2")  
  return(dat)  
}
```

2. Compare "suspect" data records to averages of other pairs.

```
checkavg<-function(dat,suspectno){
  suspect<-dat[dat$subject==suspectno,]
  rdat<-dat[,-suspectno,]
  rn<-dim(rdat)[1]
  npairs<-rn*(rn-1)/2
  res<-c(rep(0,7))
  cnt1<-0
  repeat{
    cnt1<-cnt1+1
    t1<-rdat[cnt1,]
    cnt2<-cnt1
    repeat{
      cnt2<-cnt2+1
      t2<-rdat[cnt2,]
      tsubs<-c(rdat$subject[cnt1],rdat$subject[cnt2])
      #cat("tsubs: ",tsubs,fill=T)
      tavg<-0.5*(t1+t2)
      flag1<-(tavg$ht==suspect$ht)
      flag2<-(tavg$wt0==suspect$wt0)
      flag3<-(tavg$wt1==suspect$wt1)
      flag4<-(tavg$wt2==suspect$wt2)
      nflags<-flag1+flag2+flag3+flag4
      if(nflags>0){
        tres<-c(tsubs,nflags,flag1,flag2,flag3,flag4)
        res<-rbind(res,tres)}
      if(cnt2==rn) break
    }
  }
}
```

```
    }
    if(cnt1==rn-1) break
  }
return(res)
}

#-----
summarycheckavg<-function(dat,suspectnos){
  sk<-length(suspectnos)
  res1<-NULL; res2<-NULL; res3<-NULL; res4<-NULL; res5<-NULL
  res6<-NULL; res7<-NULL; res8<-NULL
  cnt<-0
  repeat{
    cnt<-cnt+1
    tsus<-suspectnos[cnt]
    tres<-checkavgging(dat,tsus)
    rs<-dim(tres)[1]
    if(is.null(rs)==FALSE){
      if(rs==1){
        res1<-c(res1,tsus)
        res2<-c(res2,tres[1])
        res3<-c(res3,tres[2])
        res4<-c(res4,tres[3])
        res5<-c(res5,tres[4])
        res6<-c(res6,tres[5])
        res7<-c(res7,tres[6])
        res8<-c(res8,tres[7])
      }
    }
  }
}
```

```
if(rs>1){  
  cnt2<-0  
  repeat{  
    cnt2<-cnt2+1  
    ttres<-tres[cnt2,]  
    res1<-c(res1,tsus)  
    res2<-c(res2,ttres[1])  
    res3<-c(res3,ttres[2])  
    res4<-c(res4,ttres[3])  
    res5<-c(res5,ttres[4])  
    res6<-c(res6,ttres[5])  
    res7<-c(res7,ttres[6])  
    res8<-c(res8,ttres[7])  
    if(cnt2==rs) break  
  } } }  
if(cnt==sk) break  
}  
res<-data.frame(suspect=res1,other1=res2,other2=res3,nflags=res4,  
               flag1=res5,flag2=res6,flag3=res7,flag4=res8)  
res2<-res[res$other1!=0,]  
return(res2)  
}
```

3. Examine distributions of trailing digits.

```
digitdist<-function(dat){  
  ht<-dat$ht  
  wt0<-dat$wt0
```

```
wt1<-dat$wt1
wt2<-dat$wt2
ht<-floor(ht)
wt0<-floor(wt0)
wt1<-floor(wt1)
wt2<-floor(wt2)
ldht<-ht-10*floor(ht/10)
ldwt0<-wt0-10*floor(wt0/10)
ldwt1<-wt1-10*floor(wt1/10)
ldwt2<-wt2-10*floor(wt2/10)
htfs<-NULL; wt0fs<-NULL; wt1fs<-NULL; wt2fs<-NULL
cnt<--1
repeat{
  cnt<-cnt+1
  thtf<-sum(ldht==cnt)
  twt0f<-sum(ldwt0==cnt)
  twt1f<-sum(ldwt1==cnt)
  twt2f<-sum(ldwt2==cnt)
  htfs<-c(htfs,thtf)
  wt0fs<-c(wt0fs,twt0f)
  wt1fs<-c(wt1fs,twt1f)
  wt2fs<-c(wt2fs,twt2f)
  if(cnt==9) break
}
res1<-data.frame(digit=0:9,ht=htfs,wt0=wt0fs,wt1=wt1fs,wt2=wt2fs)
tstht<-sum((res1$ht-6)^2/6)
tstwt0<-sum((res1$wt0-6)^2/6)
```



```
tstwt1<-sum((res1$wt1-6)^2/6)
tstwt2<-sum((res1$wt2-6)^2/6)
pht<-1-pchisq(tstht,9)
pwt0<-1-pchisq(tstwt0,9)
pwt1<-1-pchisq(tstwt1,9)
pwt2<-1-pchisq(tstwt2,9)
res2<-data.frame(var=c("ht","wt0","wt1","wt2"),
                  tst=c(tstht,tstwt0,tstwt1,tstwt2),
                  pval=c(pht,pwt0,pwt1,pwt2))
res<-list(res1,res2)
return(res)
}
```

4. Compute influence values.

```
influencefctn<-function(dat){
  wt2<-dat$wt2
  wt1<-dat$wt1
  wtdif<-wt1-wt2
  mn<-mean(wtdif)
  v2<-var(wtdif)
  n<-length(wtdif)
  reat<-mn/sqrt(v2/n)
  subs<-NULL; infls<-NULL
  cnt<-0
  repeat{
    cnt<-cnt+1
    tsub<-dat$subject[cnt]
```

```
tvals<-wtdif[-cnt]
tt<-mean(tvals)/sqrt(var(tvals)/(n-1))
tinfl<-abs(tt-realt)
subs<-c(subs,tsub)
infls<-c(infls,tinfl)
if(cnt==n) break
}
res<-data.frame(subject=subs,influence=infls)
return(res)
}
```

Appendix 2: Data Sets Used in This Report.

1. The Flemming Data.

	subject	ht	wt0	wt1	wt2
1	63.5	164	160	157	
2	63.75	170	167	164	
3	62.75	178	176	176	
4	65	160	158.5	158	
5	65	149.5	145	139.5	
6	62.25	201.5	197.5	197.5	
7	70	214.5	212	211	
8	68.25	180	177	174	
9	64	180	177	175	
10	64.75	158.5	156.5	155	
11	67.25	176.5	173.5	173	
12	64	160	159	155	
13	65.5	220	213	211	

14 76 273 270 267
15 62 183.5 179 176
16 71 208 203.5 200
17 62.5 146 144 140
18 62.25 266.5 262 255
19 70 278.5 270.5 264
20 63.5 198.5 196.5 195
21 73.75 252 246 240
22 67.5 208 204.5 202
23 61.25 147.5 139 128.5
24 63 205 200 197
25 68 195 193 189
26 60.5 159 154 150
27 65 189 184 181
28 64.5 180 176 173
29 65 167 164 160
30 66 154 150 147
31 68 203 198.5 195
32 71 207 204 200
33 69 182 176 175
34 67.5 179 175 169
35 66.5 165.5 163 162
36 63 149 145 143
37 69 184 181 177
38 65 162 159 154
39 67 199 196 190
40 70 245 239 233

41

41 67 201 195 191
42 70 205 200 196
43 69 174 167 163
44 62.5 268 263 258
45 71 280 275 272
46 66 208 204 199
47 68 252 247 244
48 66 198 195 189
49 68 154 149 148
50 65 189 186 182
51 69 197 194 188
52 66 186 189 192
53 68 205 201 199
54 70 301 295 293
55 62 148 146 141
56 67 173 168 165
57 66 197 192 190
58 61 154 150 147
59 69 171 168 164
60 65 163 157 155

2. The Hansen Data.

subject ht wt0 wt1 wt2
1 66 180 176 173
2 62 163 160 157
3 72 232 230 230
4 68 175 173 172

5 69 180 175 169
6 73 255 251 250
7 64 175 173 172.5
8 65.5 162 159 156
9 70.5 225 222 219
10 69 180 177 175
11 72 203 200 199
12 70 180 179 175
13 71 245 238 235
14 65 207 204 201.5
15 66.5 200 196 193
16 63 157 153 150
17 74 195 193 189
18 67.5 285 281 278
19 62 225 217 211.5
20 67 165 163 162
21 72 240 234 230
22 62 175 172 170
23 68 173 165 156
24 71 253 248 245
25 61 157 155 151
26 63 177 172 168
27 73 240 235 232
28 70 206 202 199.5
29 75 223 219 214
30 69 170 166 157
31 75 248 242 238

32 60 148 145 141
33 69 184 179 178
34 64 162 158 152
35 74 205 202 201
36 68 175 171 169
37 64.5 158 155 151
38 71 204 201 196
39 69 213 209 203
40 75 260 254 248
41 70 220 214 210
42 62 158 153 150
43 65 151.5 147 143.5
44 61 253 248 248
45 72 275 277 279
46 74.5 260 256 251
47 66 230 225 222
48 69 223 220 215
49 64 129 125 124
50 60 159 156 153
51 71 213 209 203
52 70 207 205 204
53 63 178 174 172
54 68 278 272 270
55 73 210 208 203
56 72 191 185 182
57 69 212 207 205
58 70 203 199 196

59 70.5 177 174 170

60 61 148 143 141

3. The Simulated Data.

subject	ht	wt0	wt1	wt2
---------	----	-----	-----	-----

1	67.5	207	202	200
---	------	-----	-----	-----

2	62	161	161	161
---	----	-----	-----	-----

3	70	269	263.5	254
---	----	-----	-------	-----

4	65	188	184	181
---	----	-----	-----	-----

5	69	249	244	237
---	----	-----	-----	-----

6	67	166.5	162	157
---	----	-------	-----	-----

7	75	211	208	204
---	----	-----	-----	-----

8	66	208	205	202
---	----	-----	-----	-----

9	65	205.5	200	196
---	----	-------	-----	-----

10	66	206	200	197
----	----	-----	-----	-----

11	65	181	178.5	174
----	----	-----	-------	-----

12	66	200.5	196	192
----	----	-------	-----	-----

13	66	171	168.5	167
----	----	-----	-------	-----

14	71	235	232	231
----	----	-----	-----	-----

15	66	179	173	170
----	----	-----	-----	-----

16	61	161	157	155
----	----	-----	-----	-----

17	63	179	175.5	174
----	----	-----	-------	-----

18	72	147	145	143
----	----	-----	-----	-----

19	70	231	225	220
----	----	-----	-----	-----

20	63	136	132.5	125
----	----	-----	-------	-----

21	63.25	217.5	213	212
----	-------	-------	-----	-----

22	69	236	231	226
----	----	-----	-----	-----

23 67 171 166 162
24 71 193 188 186
25 67.5 174 169.5 166.5
26 72.5 265.5 258 254
27 65 214 211 207
28 65 185 180.5 180
29 63 192.5 189 184
30 67 231 227.5 224
31 65 192 188 185.5
32 67 218 217 216
33 63.5 184 177 168
34 65.75 222 215 209.5
35 67 207 201 196
36 66.5 257 256 254
37 72 223 218 212
38 71 221 214 210
39 66.25 213 209 206
40 66 239.5 236 233
41 67 143 140 137
42 64.25 221 216 211
43 66 209 203 198
44 68.25 181.5 179 177
45 69.5 243 234 229
46 70 252 247 242
47 64 158 156 155
48 68 222 220.5 215
49 70.5 257 249 242

46

50 69.75 219 216 212
51 69.25 156.5 154 150
52 68 191 187 184
53 64.5 182 180 174
54 73.75 252 247 242
55 70 194.5 190 186
56 61 210.5 206 204
57 68.5 265 257 253
58 62 187 182 177
59 71.75 198 192 188
60 64 145 142 140